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RESPLITTING SPLIT-THICKNESS GRAFTS WITH THE DERMATOME

A METHOD FOR INCREASING THE YIELD OF LIMITED DONOR SITES

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THE MANAGEMENT of a large skin defect is often a difficult problem because of a limited amount of available donor skin. Methods heretofore used to cover large skin defects, namely, pinch grafts and postage stamp grafts, are not entirely satisfactory because of relatively poor cosmetic results and because of the additional time required for epithelization between the grafted areas. Split-thickness grafts produce a good cosmetic effect but the area that can be covered is limited by the available donor skin area.

It is important that large skin defects be covered as rapidly and as completely as possible. It is known that patients with extensive burns lose large amounts of nitrogen. In Hirshfeld's[1] studies upon burned patients he found that even though the patients were encouraged to eat a high protein, high carbohydrate diet, they only ingested about 60 per cent of their protein requirements. Taylor and his associates,[2] have demonstrated the large amounts of protein required to keep severely burned patients in nitrogen balance. The nitrogen loss is so great that malnutrition is now regarded as one of the causes of death in severely burned patients. This nitrogen loss, or protein destruction, apparently disappears as soon as the burned areas are epithelized. Early complete grafting of large skin defects will undoubtedly reduce morbidity and mortality.

In a limited number of cases the "split-split" graft, which would enable one to cover a large skin defect with a relatively small amount of donor skin and which gives a satisfactory cosmetic result has been quite successful

The principle of the method is simply the splitting of a Padgett[3] skin graft into layers. The donor skin is cut as thick as possible without interfering with the regeneration of the epithelium of the donor area. In adults this depth ranges from 0.020 to 0.028 of an inch. In the case of children, and when the abdomen or medial surface of the thigh is used in women, the depth of the graft is limited to between 0.012 and 0.018 of an inch.[3] When the graft has been cut and the skin is still adherent to the dermatome drum,

the knife blade is adjusted to one-half the original distance from the drum. Rolling or separation of the leading edge of the skin from the dermatome is prevented by passing over the first quarter of an inch of skin before adjusting the knife blade to the proper distance for resplitting the skin. By repeating the cutting process the graft may be split into two layers. One must be sure that the knife edge is flat and that it is exactly parallel to the surface of the drum, otherwise the knife will tend to pull the skin away from the surface of the drum. At times it is possible to cut a Padgett graft into three layers.

FIG. 1.—Skin 0.016-inch thick still adherent to the Padgett dermatome is being split into two layers each 0.008-inch thick.

Thus, the skin from a given donor area can be used to cover an area 200 to 300 per cent as large. The individual "split-split" grafts may vary in thickness from 0.006 to 0.012 inches.

FIG. 2.—A. Grafts applied to the leg of burned child. The graft in the region of the thigh is the outer thickness of a "split-split" graft 0.008-inch thick. On the popliteal region is an ordinary Padgett graft 0.016-inch thick. The region of the calf is covered with the inner thickness of a "split-split" thickness graft 0.008-inch thick.

B. All three areas of grafts have taken 100 per cent on the tenth postoperative day. The raw area in the region of the calf is the result of too early removal of the paraffin gauze. When the paraffin gauze was removed a thin layer of epithelium was removed with the gauze. The deeper epithelial elements are clearly seen.

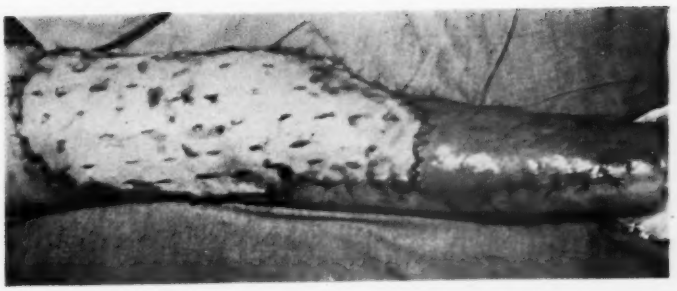
C. Appearance of grafts four weeks later. All areas have been completely epithelized. Raw areas seen in the region of the ordinary Padgett graft as well as in the regions of the "split-split" grafts, are the result of secondary infection. These raw areas were at one time epithelized as can be seen in B.

FIG. 3.—A. "Split-split" grafts may also be used as postage stamp grafts. The postage stamp grafts from the inner layer of the "split-split" grafts have been applied over the right half of the ulcer as it appears in the photograph and outer layer of the "split-split" grafts over the left half of the ulcer of the buttock.

B. Appearance of the same grafts five days later.

C. Complete healing three weeks later.

FIG. 4.—Typical "split-split" donor area three weeks after cutting of the graft.



2A

2B

2C

3A

3B

3C

FIG. 4

The take of the inner layer of a "split-split"-thickness graft produces a result which is quite similar to the healing Padgett donor area. During the first ten or twelve days both of these areas are covered with a thin sheet of epithelial cells. This delicate epithelial layer is easily injured by frequent dressings. We have learned to dress the donor area with paraffin gauze and leave the innermost layers of the dressings in place, literally, until they fall off, which is usually at the end of two weeks. The "split-split" grafts like the donor areas are covered with two layers of paraffin gauze. A pressure dressing of ordinary gauze is then applied over the paraffin gauze. The grafted area is not touched until the tenth postoperative day. At this time the outer dressings are removed. If the grafts are not infected the paraffin gauze is not removed for fear of injuring the delicate new epithelial layer. The paraffin gauze may be removed without danger of injuring the new epithelium after the fifteenth to sixteenth postoperative day.

"Split-split" grafts have been employed on six patients. In one of these patients, the result was classed as a failure, although parts of the grafts did take. In this same patient a subsequent simple Padgett graft was equally unsuccessful. In the remaining five cases 90 to 100 per cent of the grafts remained viable. The outer layers and the inner skin layers took equally well. The period required for the inner layer to become completely healed is slightly more prolonged than that required for the outer layer of the skin. This is due, probably, to the fact that the outer layer of skin is completely keratinized at the time of the application of the graft, whereas the inner layer is not.

Some operators have failed to obtain satisfactory results with the Padgett dermatome. Since we have adopted a rigid technic for preparing the skin and the dermatome drum, we have not failed to obtain complete grafts. Two factors seem important. The first is a clean, fat- and moisture-free skin surface. The second is the time factor which is necessary to allow the dermatome (rubber) cement to set before the actual cutting is attempted.

In preparation of the donor skin the area must be closely shaved (preferably with a straight razor) and then be washed with soap and thoroughly rinsed with water either in the patient's room or in the operating room. In the operating room the area is treated with alcohol followed by several liberal applications of ether. Special skin preparations and preparations containing dyes or bichloride of mercury have been carefully avoided for fear that they might leave a thin film or precipitate on the skin which would interfere with the efficiency of the dermatome cement. Each application of alcohol and ether is combined with vigorous scrubbing of the skin with a gauze sponge on a sponge stick. The ether assures one of the adequate removal of all fatty material. It may also act locally to cool the skin so as to inhibit excretion of the sweat glands temporarily. Perspiration may lift

the cement away from the skin surface sufficiently to prevent the adherence of the skin to the dermatome drum.

The cement must be allowed to set or partially dry before the actual cutting is attempted. "Haste makes waste" were never truer words than in the cutting of Padgett grafts. Five to ten minutes are allowed for the setting or partial drying of the cement. The dermatome drum may even be painted before the patient is anesthetized.

Another possible cause of failure of adherence of the cement is the application of the cement to a recently autoclaved dermatome which is still warm. The heat of the drum will cause the rubber solvent to boil and form bubbles in the cement. If bubbles form in warm weather the drum should be cleansed with ether and then two very thin layers of cement should be applied. Care should be taken that one layer of cement is quite dry before another is applied. The cement-covered skin and drum should not be touched for fear of removing some of the cement.

When the layers of cement have dried sufficiently the leading edge of the drum is firmly applied to skin for at least one minute by the clock. The drum must not be twisted or rocked upon the skin lest some of the cement become detached from the skin or drum. The cutting should be done slowly, in order to provide ample time for the skin to become firmly adherent to the rolling drum surface. Short even strokes of the knife blade are used to cut the skin. Wide excursions of the cutting knife tend to separate the skin from the drum. If the foregoing rules are observed a complete drum of skin can be easily removed.

SUMMARY

1. A method of splitting ordinary Padgett split-thickness skin grafts is described.

2. Certain details of the technic for the use of the dermatome are presented which enable us, consistently, to obtain a full drum of skin.

3. By using "split-split"-thickness grafts areas which are 200 per cent to 300 per cent larger than the donor area, can be epithelized.

4. The inner layer of a "split-split"-thickness graft becomes completely epithelized in about the same period of time required for epithelization of the Padgett donor area.

5. In five of six patients 90 to 100 per cent of the "split-split"-thickness grafts remained viable. One case in which an ordinary Padgett split-thickness graft was unsuccessful, "split-split" thickness grafts were also unsuccessful.

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COMPARATIVE STUDIES OF CANCEROUS VERSUS NONCANCEROUS BREASTS

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I. BASIC MORPHOLOGIC CHARACTERISTICS

THE PRESENT STUDY represents an effort to determine whether fundamental structural differences exist in the breast tissue of women who do have mammary cancer and those who do not have this disease. In other words, the main objective has been to ascertain if there is any characteristic "soil" in which mammary carcinoma is apt to develop. Another interest has been to search for abnormalities in these breasts that could be referred to certain hormonal influences, and finally an attempt has been made to evaluate the relationship between so-called chronic cystic mastitis and mammary cancer. The investigation was not begun with any preconceived point of view concerning these problems, and it has been constantly borne in mind that little positive information might be secured. A study of this sort necessarily enters into debatable matters about which a vast literature has accumulated. Due to the large volume of such literature, reference can be made only to specific papers which seem most pertinent to the findings under discussion.

The material for comparative gross and microscopic analysis was secured during 1940 from operations performed on the Breast Service at the Memorial Hospital. It consisted of 300 cancer-containing breasts from radical mastectomies and 200 specimens of noncancerous breast tissue from partial mastectomies or very occasional simple mastectomies. The material was sectioned specifically for this planned study, and in every case both normal and abnormal appearing tissues were embedded. No selection of cases was made with the following exceptions: No irradiated breast was included. A few cases were excluded in which there was total or near total replacement of the breast tissue by carcinoma. In the cases of local excision, it was required that the mass of breast tissue be large enough to furnish satisfactory representative sections. Thus, it was necessary to exclude a small number of assorted noncancerous lesions excised with a margin too small for our purposes. Finally, no case was included in which the operation was undertaken for pyogenic or specific infection of the breast.

We recognize the disadvantage of comparing the findings in complete mastectomies with findings in partial mastectomies. This disproportion in tissue mass, however, is largely compensated for, since in doing a local excision, the surgeon may be expected to select the most obviously abnormal portion of the breast and is careful to remove a margin of less involved or uninvolved tissue. So, if a gross abnormality is present it appears likely that it will be removed. In order to balance microscopic findings as much as possible, compar-

able amounts of grossly unaltered tissue were embedded in both the cancer and the noncancer cases. The total mass of tissue embedded in the two groups of cases has been equal in amount exclusive of the cancer itself.

In this survey the following plan of analysis was employed: Each case was tabulated for the presence or absence of specific lesions, so that composite percentage figures for each of the two types of cases were secured. The two general groups were then subtabulated, decade by decade, to enable proper comparison, since the influence of age in the frequency of certain lesions is so great that this must be insisted upon in interpreting results. For closer analysis of certain specific lesions, it was then considered necessary to tabulate other lesions that occurred in unison with the particular one under examination. By this method it is possible to learn the sort of histologic environment in which a given lesion is apt to be found and it permits one to detect trends in occurrence that indicate fundamental interrelationships, or their lack. By no means do the figures given for the incidence of certain lesions imply that they represent absolute values. The frequency of microscopic lesions can always be elevated somewhat by embedding innumerable blocks. Terminology in breast lesions is by no means standardized. Where commonly employed terms are used, effort has been made to define our own usage of these, and where unaccustomed ones are used, special effort has been made to describe the lesions in full.

The average age of the 300 cancer cases was 49.5 years, that of the 200 noncancer cases 39 years. The distribution by decades is shown below.

TABLE I

Decade	Cancer Cases	Noncancer Cases
10–20		4
20–30	3	30
30–40	54	68
40–50	104	78
50–60	66	16*
60–70	60	3
70+	13	1
Total	300	200

* In tabular analyses that appear in succeeding sections, comparative histologic findings are given for the third, fourth, and fifth decades. Since the series of 200 noncancerous breasts contained only 16 cases in the fifth decade, 24 consecutive noncancerous breasts were added to this group, so that observations are based on the more significant number of 40 cases.

Subjects to be discussed will appear in the following order:

I. Factor of atrophy
II. Cysts
III. Duct papillomatosis
IV. Blunt duct adenosis
V. Apocrine epithelium
VI. Sclerosing adenosis
VII. Periductal mastitis
VIII. The mammary lobules
IX. Relation of so-called chronic cystic mastitis to mammary cancer
X. Histologic findings in breasts after administration of estrogenic substance

I — FACTOR OF ATROPHY

Inasmuch, as mammary cancer occurs most frequently in breasts that are beginning to undergo atrophy, or are already in varying degrees of this state, can any differences in this process be found in cancerous as opposed to noncancerous breasts? The principal feature in atrophy of the mammary gland is reduction of its parenchyma to an extent that is much more complete than in most organs. Atrophy begins at the lobular terminations of the duct system and proceeds toward the nipple so that the end-result is near, or total, loss of lobules and more or less diminution of the terminal and small ducts. Extreme variations in the degree of atrophy can be seen in individuals of the same age-group, and occasionally breasts are seen that maintain the integrity of their lobules for surprisingly long periods beyond the menopause. As an illustration, we have recently studied sections from a surgical excision done three years after the menopause. In this case the lobules were not only very numerous but they possessed abundant acini, and, here, mitoses were found in surprisingly large numbers. In the absence of various quantitative and qualitative metabolic determinations, no explanation attempted could be supported. The patient had a strong family history of mammary cancer. In atrophy of the breast other changes, such as loss of periductal myoid, duct dilatation, fatty replacement of fibrous stroma, and subsidence of certain proliferative and cystic lesions, accompany the decreasing number of mammary lobules.

An estimate of the number or frequency of the mammary lobules is the most convenient index for estimating atrophy. No very exact method of estimating the number of lobules seems required, nor is it reasonably possible, and we have merely listed cases as having "numerous," "average" or "few" lobules. Table II shows the frequency of lobules in the cancer and noncancer cases as separate whole groups and also shows a comparison by decades.

TABLE II

	Number of Lobules		
	Numerous	Average	Few
200 noncancer cases	13%	61%	25%
300 cancer cases	8%	36%	56%
Noncancer cases, age 30–40	10%	60%	30%
Cancer cases, age 30–40	10%	51%	39%
Noncancer cases, age 40–50	12%	55%	33%
Cancer cases, age 40–50	10%	57%	33%
Noncancer cases, age 50–60	3%	25%	72%
Cancer cases, age 50–60	3%	27%	70%

The only significant discrepancy shown is in the lobule frequency of the two types of cases when compared as whole groups. This is at once referable to the greater average age of the cancer-containing breasts, since, in equivalent decades, there is close uniformity. It appears justifiable to state the obvious conclusion that mammary lobules are not more or less numerous in cancerous than noncancerous breasts in the same age-group.

It may be inquired if any of the common proliferative lesions of the breast

tend to persist in cancerous breasts and disappear from noncancerous breasts, presumably supplying a possible source for the development of cancer. This is given a negative answer in other sections of this paper where these lesions are shown to regress sharply in the 50- to 60-year decade.

The question of the relation of mammary atrophy to mammary carcinoma is of very considerable speculative interest. It is of interest from at least two viewpoints: Certain it is that atrophy is a precursor of cancerization in certain tissues, although causal relationship of such atrophy to cancer is not clear. Our observations as regards mammary atrophy fail to indicate that such atrophy is significantly more frequent in the cancerous breast when compared to the noncancerous breast of similar age. The second point of interest concerns the question of hormone etiology of mammary cancer. Where those hormones which presumably are concerned with mammary lobule growth or persistence concerned in a major way with mammary cancer development, one might at least expect some difference in lobular status in the cancerous versus the noncancerous breast; that is, one might anticipate the finding of greater lobule abnormality outside the actual cancerous area in the cancerous breast than in the "normal" for the age-group. This matter will be discussed in some detail in a later section pertaining specifically to lobule structural patterns.

II — CYSTS

Included in these tabulations are only those cysts visible to the naked eye, and, hence, those cysts measuring from about one millimeter upwards in diameter are represented. It is our belief that if one reports on microscopic cysts, serial sections are required to prove complete isolation and loss of communication with adjacent ducts or lobules. If microscopic lesions that appear cystic are included, it is inevitable to confuse, in some measure, blunt end ducts, dilated ducts or distended lobule components. No lesion was included as a cyst unless it was an isolated structure distended with fluid and totally separate from duct and lobule system. The figures will not separate cases with solitary cysts from those with multiple ones, since in both types of material the solitary cysts, whether large or small, were so few as to be insignificant.

In the 200 noncancerous breasts, cysts as qualified in the preceding statements were found in 106, or 53 per cent. Of the 300 cancer breasts, 82, or 27 per cent, contained cysts. The average age of the benign cases with cysts was 41.1 years and in the cancer cases with cyst, the average age was 48.4 years. When the occurrence of cysts is studied by decades, the following is seen (Table III).

TABLE III

Decade	Comparative Frequency of Cysts in Noncancerous Cases	Cancer Cases
30–40	52%	34%
40–50	65%	18%
50–60	30%	25%

Accordingly, it is obvious enough that cysts are distinctly more characteristic of noncancerous than cancerous breasts. Indeed, in the decade 40–50,

which is the most common ten-year period for the appearance of mammary cancer, they are less than one-third as frequent in cancer-bearing breasts as in breasts free from cancer. Cysts, like many other lesions of the breast, may appear at a relatively early age, but are often transient structures and they become decreasingly numerous as old age is reached. Observations extended beyond the age of 60 (in material additional to that studied here) show that between 60–70 years of age, the incidence of cysts in both cancerous and noncancerous breasts falls sharply. Statistically, cysts seem to play a negative rôle in mammary cancer. The lower incidence of cysts in cancer-bearing breasts cannot be explained by the supposition that the cysts are replaced by the cancers, for morphologic evidence is directly opposed. In tracing the genesis of mammary cancer, one finds true intracystic carcinoma to be one of the rarest morphologic types. Terminology in breast pathology is so loose that the term "intracystic" is often employed when the proper designation is "intraductal." This common practice has led to much confusion as to the frequency of intracystic cancers as well as intracystic papillomas. If one studies the walls of cysts he finds with extreme rarity any evidence of atypical or other epithelial proliferation. It is actually much more common to find no epithelial lining at all. In the 300 cases of mammary cancer under consideration here, only two could be shown convincingly to have arisen in a cyst.

The question may be raised as to what other lesions are apt to be found in breasts that contain cysts and if the same lesions appear regardless of whether the breast is or is not cancer-containing. For making these determinations, all of the cyst-bearing breasts were tabulated for the presence or absence of 14 definite histologic characters. In Table IV are also shown figures for the frequency of these lesions as they occurred in the entire group of 200 cases without cancer and the 300 cases with cancer.

TABLE IV

	Frequency of Various Lesions in			
	106 Noncancer, with Cysts	200 Consecutive Cancers	82 Cancers, with Cysts	300 Consecutive Cancers
1. Hyperplasia of duct epithelium	52%	39%	80%	57%
2. Duct papillomatosis	42%	29%	50%	36%
3. Intracystic papilloma	2%	2%	1%	1%
4. Blunt duct adenosis	40%	26%	40%	26%
5. Apocrine epithelium	67%	42%	57%	39%
6. Sclerosing adenosis:				
A. Diffuse	1%	1.5%	2%	0.3%
B. Focal	18%	11%	13%	7%
7. Fibro-adenoma	9%	19%	10%	7%
8. Tendency to fibro-adenoma	5%	3%	8%	6%
9. Stasis and distention of ducts	41%	36%	62%	42%
10. Duct metaplasia	42%	34%	62%	45%
11. Periductal mastitis	23%	22%	20%	14%
12. Fat necrosis	1%	2%	2%	1.3%
13. Lobule frequency:				
Numerous	14%	13%	10%	10%
Average	62%	61%	41%	35%
Frequent	24%	26%	49%	55%
14. Periductal myoid atrophy	31%	27%	56%	42%

From Table IV a general summary may be drawn that no obvious qualitative divergence is detectable when comparing the noncancerous elements of cancer-containing breasts with breast tissue removed surgically from noncancerous breasts when the common denominator of each group is the presence of one or more cysts. True enough, there are certain quantitative differences of lesser degree which are substantially diluted when the factor of age is considered. Cysts may be regarded as relatively passive structures representing essentially the end-phase of a pathologic process. Characteristically, they are accompanied by a group of what may be termed proliferative processes somewhat more numerous than the proliferative processes seen in a general average of breasts when these proliferative processes are enumerated with disregard of the presence of cysts.

It is of interest to compare the lesions in noncystic breasts with the findings just recorded for cystic breasts of both benign and cancerous breasts.

TABLE V

	Frequency of Various Lesions in			
	106 Noncancer, with Cysts	94 Noncancer, without Cysts	82 Cancers, with Cysts	218 Cancers, without Cysts
1. Hyperplasia of duct epithelium	52%	23%	80%	48%
2. Duct papillomatosis	42%	14%	50%	31%
3. Intracystic papilloma	2%	2%	1%	1.5%
4. Blunt duct adenosis	40%	9%	40%	20%
5. Apocrine epithelium	67%	14%	57%	32%
6. Sclerosing adenosis:				
A. Diffuse	1%	1%	2%	0%
B. Focal	18%	6%	13%	4%
7. Fibro-adenoma	9%	30%	10%	6%
8. Tendency to fibro-adenoma	5%	5%	8%	5%
9. Stasis and distention of ducts	41%	28%	62%	34%
10. Duct metaplasia	42%	25%	62%	39%
11. Periductal mastitis	23%	19%	20%	12%
12. Fat necrosis	1%	3%	2%	1%
13. Lobule frequency:				
Numerous	14%	12%	10%	11%
Average	62%	52%	41%	35%
Frequent	24%	36%	49%	64%
14. Periductal myoid atrophy	31%	22%	55%	36%

Table V emphasizes in greater contrast than the preceding one the tendency of certain lesions to occur in cyst-containing breasts irrespective of the presence of cancer. These lesions include hyperplasia of duct epithelium, duct papillomatosis, blunt duct adenosis, apocrine epithelium and sclerosing adenosis. All of these can be regarded as proliferative or hyperplastic in nature. It should be noted that fibro-adenoma fails to follow this tendency and in the benign group is actually reversed. Fibro-adenoma must be regarded as a proliferative lesion, but it seems to be of a different order from other mammary proliferations. Also to be noted is the greater frequency in cyst-containing breasts of lesions designated as "stasis and distention," "duct metaplasia," "periductal myoid atrophy" and "periductal mastitis." That these are secondary phenomena dependent upon pressure and obstructive factors will be explained in a section to follow.

III — DUCT PAPILLOMATOSIS

Under this designation are included all stalked papillary adenomas. These are usually found in the large- or medium-sized ducts and are usually macroscopic. Also, included here are cases with partial or complete epithelial plugging of the smaller stems of the duct system. These lesions are often seen with no vascular stalk, and it is admitted that they are not papillary adenomas in the strictest sense of the word. They are, however, papillary in a modified sense and of distinctly greater magnitude than lesions spoken of here as simple hyperplasia of duct epithelium. In a large part they are microscopic and almost invariably multiple. They are present in many more cases than are the macroscopic stalked papillomas, but in nearly every case where a stalked papilloma is present these lesions can be found in some other portion of the breast tissue. No universally accepted standard exists for the lower level of epithelial hyperplasia where one ceases to use the term papillomatosis, and any division must be more or less arbitrary. Undoubtedly, writers on breast pathology do not uniformly conform in terminology. It is our belief, that in the material here, a relatively strict interpretation is made, and that in many other hands the figures for the papillary lesions might be considerably higher. In any event, the same level of inclusion or exclusion is adhered to when enumerating these papillary lesions in the two types of material under examination here. The stress is always to compare the same kinds of lesions. Emphasis is again made that in this section we are considering papillary lesions that are intraductal in location, and the statement is repeated that true "intracystic papillomas" are of very uncommon occurrence. It would be necessary to have several thousand consecutive cases of cancerous and noncancerous breasts to yield a sufficiently large number of true intracystic papillomas before adequate comparisons could be made.

In the series of 200 breasts without cancer, duct papillomatosis was found in 58, or 29 per cent. In the 300 breasts containing cancer, this finding was made in 108, or 36 per cent. It should be noted that the figures quoted would be appreciably elevated if papillary hyperplasias of pink-staining apocrine epithelium were included. Foci of apocrine epithelium are sometimes found in a papilloma, to be sure, but no case was included in which the papillary element was solely apocrine. The mammary apocrine element is discussed in a separate section. Although repetitive, the statement is emphasized that the lesions recorded here as constituting papilloma or papillomatosis are not minimal in nature, and would certainly be regarded by any reasonable observer as meriting the dignity of the term.

The occurrence of papillomas by decades in recorded in Table VI.

TABLE VI

Decade	Frequency of Duct Papillomatosis in Noncancerous Cases	Cancer Cases
30–40	18%	24%
40–50	40%	40%
50–60	23%	28%

Table VI indicates no very great difference in the frequency of duct papillomatosis in the two types of material under analysis when equivalent age-groups are considered. The somewhat higher figure, 36 per cent for duct papillomatosis in the entire series of 300 cancerous breasts against the figure 29 per cent for 200 noncancerous breasts is, likewise, not of sufficient degree to indicate more than a trend.

If no impressive difference in frequency, then, is there a difference in the kind of papillomatosis? This may be ascertained from the following comparisons:

1. Are macroscopic papillomas more common to one group than the other? Analysis shows that of the 58 benign breasts with papillomas, 14, or 26 per cent, were greater than 1 mm. in diameter. Of these 14 cases of macroscopic papillomas, six showed additional foci of microscopic papillomatosis. Of the 108 cancerous breasts with papillomas only eight, or 7 per cent, were macroscopic, and in each of these eight cases additional foci of microscopic papillomatosis were found. These findings are not startling, and can be summarized by stating that macroscopic papillomas are more characteristic of benign than cancerous breasts, and that "solitary" macroscopic papillomas are decidedly accented in this group. In passing, it can be said that the bulk of the macroscopic papillomas falls between the ages 50–60, but extremes below 30 and beyond 60 occur.

2. Is there a difference in the "degree" of the papillomatosis of cancerous and noncancerous breasts? The term "degree" is used here to designate the multiplicity of the lesions and is qualified by the relative terms marked, moderate and slight.

TABLE VII

DEGREE OF PAPILLOMATOSIS

	Slight	Moderate	Marked
Noncancer group (58).....	31, or 53%	16, or 27%	11, or 20%
Cancer group (108).....	69, or 64%	27, or 25%	12, or 11%

Again, nothing very impressive is seen in the comparative figures. The above grouping by "degree" does not take into special account the minute histology of the single cells.

3. Are the papillary lesions of one group more or less apt to be atypical, histologically, than in the other? The term "atypical" here indicates a disturbance in cell uniformity and includes the usual traits such as altered stainability, variation in size and/or shape, and loss of polarity. All of these characters are subject to much variation ranging from trivial alteration to a stage where they merge imperceptibly with the histology of cancer. When a case is called "atypical" it signifies that it is at least of a certain substantial level of atypism. No effort is made to classify beyond this arbitrary line. In the 58 cases of papillomatosis from noncancerous breasts only five were considered atypical while in the 108 cancer-containing breasts, the papillomatosis was considered atypical in 45. It is emphasized that the lesions

were not part of a cancer. The far higher incidence of atypical papillomatosis in cancerous breasts is one of the few outstanding differences recorded in this comparative study. It is a qualitative difference about five times more common in cancer-containing breasts. The contrast is made more obvious by recalling that orderly papillomatosis is almost as common in one type of material as the other.

Table VIII shows the lesions that occur in unison with papillomatosis. For purposes of comparison the table includes the absolute frequency of the same lesions as they occurred in the two groups as a whole.

TABLE VIII

LESIONS ACCOMPANYING DUCT PAPILLOMATOSIS

	58 Noncancer Cases, with Duct Papillomatosis	200 Consecutive Noncancer Cases	108 Cancer Cases, with Duct Papillomatosis	300 Consecutive Cancer Cases
1. Hyperplasia of duct epithelium	90%	39%	95%	57%
2. Intracystic papilloma	4%	2%	1%	1%
3. Blunt duct adenosis	62%	26%	49%	26%
4. Apocrine epithelium	63%	42%	50%	39%
5. Sclerosing adenosis:				
A. Diffuse	2%	1.5%	1%	0.3%
B. Focal	16%	11%	13%	7%
6. Fibro-adenoma	8%	19%	4%	7%
7. Tendency to fibro-adenoma	10%	3%	4%	6%
8. Cysts	74%	53%	32%	27%
9. Stasis and distension of ducts	56%	34%	53%	42%
10. Duct metaplasia	48%	34%	64%	45%
11. Periductal mastitis	36%	22%	16%	14%
12. Fat necrosis	0	2%	1%	1.3%
13. Lobule frequency:				
Numerous	12%	13%	10%	10%
Average	62%	61%	40%	35%
Few	26%	26%	50%	55%
14. Periductal myoid atrophy	54%	27%	52%	42%

The percentage differences are nowhere great enough to show any fundamental difference in the lesions that accompany papillomatosis in cancerous as opposed to noncancerous breasts—at least no difference that is not manifest in these two groups taken as a whole. It is of distinct interest to note again the tendency of certain cystic and proliferative lesions to occur in unison—cysts, hyperplasia of duct epithelium, duct papillomatosis, blunt duct adenosis, apocrine epithelium and sclerosing adenosis. Each of these lesions has been, or will, be discussed from the point of view of what morphologic part they seem to play in mammary carcinogenesis. Attention is called, again, to the failure of fibro-adenoma, another proliferative lesion, to be found concomitantly with the other lesions just mentioned, further suggesting that fibro-adenoma is a different proliferative manifestation. In the section on cysts, factors influencing the frequency of periductal mastitis and associated lesions have been mentioned, and no further comment will be made until this group is separately dealt with.

A further means of comparing the cancerous and noncancerous series is afforded by tabulating the preceding group of 14 lesions as they occur in the absence of duct papillomatosis.

TABLE IX

COMPARATIVE FINDINGS IN BREASTS WITH AND WITHOUT DUCT PAPILLOMATOSIS

	58 Noncancer Cases, with Duct Papillomatosis	142 Noncancer Cases, without Duct Papillomatosis	108 Cancer Cases, with Duct Papillomatosis	192 Cancer Cases, without Duct Papillomatosis
1. Hyperplasia of duct epithelium	90%	23%	95%	35%
2. Intracystic papilloma	4%	1%	1%	1.5%
3. Blunt duct adenosis	62%	14%	49%	13%
4. Apocrine epithelium	63%	35%	50%	33%
5. Sclerosing adenosis:				
A. Diffuse	2%	1%	1%	0.5%
B. Focal	16%	11%	13%	3%
6. Fibro-adenoma	8%	23%	4%	9%
7. Tendency to fibro-adenoma	10%	3%	4%	7%
8. Cysts	74%	44%	32%	25%
9. Stasis and distention of ducts	56%	27%	53%	36%
10. Duct metaplasia	48%	28%	64%	31%
11. Periductal mastitis	36%	17%	16%	13%
12. Fat necrosis	0	3%	1%	1.5%
13. Lobule frequency:				
Numerous	12%	13%	10%	10%
Average	62%	67%	40%	33%
Few	26%	27%	50%	57%
14. Periductal myoid atrophy	54%	17%	52%	36%

In Table IX the same trends as formerly noted are repeated in sharper contrast. Regardless of whether breasts do or do not contain a cancer, they tend to maintain similar structure when cross-examined on the basis of possessing a common histologic factor such as presence or absence of duct papillomatosis. As the noncancerous proliferative lesions of cancerous breasts are analyzed, it begins to be apparent that the pattern of the breast tissue is more influenced by the presence or absence of these noncancerous lesions than by the presence of the cancer itself.

The direct part played by duct papillomatosis in the morphogenesis of cancer of the breast cannot be stated in very exact terms. In contrast to cysts and other common lesions, however, there is ample evidence of a far more direct relationship. In the 300 mammary carcinomas studied here, there were 45 examples of atypical papillary hyperplasia with various degrees of change bordering on the histology of cancer. In over one-half of the 300 cancers, there was evidence of duct origin represented by papillary or stratified intraductal foci of tumor. In the remainder of these mammary carcinomas the duct origin could not be satisfactorily traced, but by far the greatest number had the histologic traits usually seen in infiltrating duct carcinoma. In a small number of cases, lobule origin was apparent (about one in 25), and in still another small group simultaneous duct and lobule participation seemed present. The traceability of mammary cancer to any structure but the mammary ducts is uncommon, so that any theory of carcinogenesis in the human female breast must necessarily concern itself principally with lesions of the duct system. The commonest abnormality of the duct epithelium is papillary or near-papillary hyperplasia, and every conceivable transition can be noted to *in situ* or infiltrating cancer. Since the

usual mammary carcinoma is fully developed and advanced when it comes under observation no one can say what percentage of these cancers develops on a basis of papillomatosis, but it can be said that this basis does exist for some of the cases, and it is rare to find any early duct cancer of the breast in the absence of atypical papillomatosis.

The fact previously noted that atypical papillomatosis is seldom seen in noncancerous breasts is the only impressive difference shown so far. The actual number of papillary lesions that eventually become mammary cancers must necessarily be a very minute fraction, and we know of no way at the present to prognosticate the probable course of any given histologic type. It is certain that most of these lesions disappear from the breast, and in the material studied here there are many examples of the retrograde phases of these lesions, namely, varying degrees of abortive fibrosis with gradual obliteration of epithelial component. Now and then, however, one will find an area of papillomatosis in which the hyalinosis is apparently interrupted by a new surge of epithelial hyperplasia which may or may not show histologic atypism. This observation prompted the query as to whether or not a characteristic of cancerous breasts was persistence of papillary lesions. This is answered in the negative by noting that both noncancerous and cancerous breasts between ages 40–50 have papillary lesions in the same frequency—40 per cent; and the corresponding figures for the ages 50–60 are 23 per cent for noncancerous and 28 per cent for cancerous breasts. In the noncancer group the 58 cases of papilloma included five that were histologically atypical. This number is entirely too few to ascertain if age influences atypicalness, and no conclusion can be drawn from their occurrence at ages 48, 43, 55, 41 and 46. In the cancer cases with atypical papillomatosis, the age curve is practically identical with the age curve of the cancer cases with nonatypical papillomatosis, and in addition the same age curve is followed by the nonatypical papillomatosis of the noncancer series of cases.

To illustrate transitions from orderly duct papillomatosis to mammary carcinoma is not difficult if samples are selected from several cases, but the entire gamut of alteration occurs only in the exceptional single case. Such a case with step-like histologic sequences is shown in Figures 1 through 8.

IV — BLUNT DUCT ADENOSIS

Blunt duct adenosis is a term we have used to designate one of the common proliferative lesions of the breast. Although it is undesirable to invent new terms, nevertheless, this designation expresses the principal characteristic of these structures, namely, that they are ducts which end abruptly and do not terminate in lobules. The origin, course and termination of these blunt end ducts can be traced easily in serial sections. It was after this sort of study that it became obvious that one cannot rely upon a single microscopic section in deciding whether a given structure is a minute cyst or not; hence the limiting of tabulation of cysts in this paper to cysts of

macroscopic proportion. Blunt end ducts usually originate at the distal or near distal extremities of the duct system, and since they begin at a point where periductal myoid tissue is absent or markedly attenuated, they typically lack this myoid investment and have a relatively poorly developed

FIG. 1

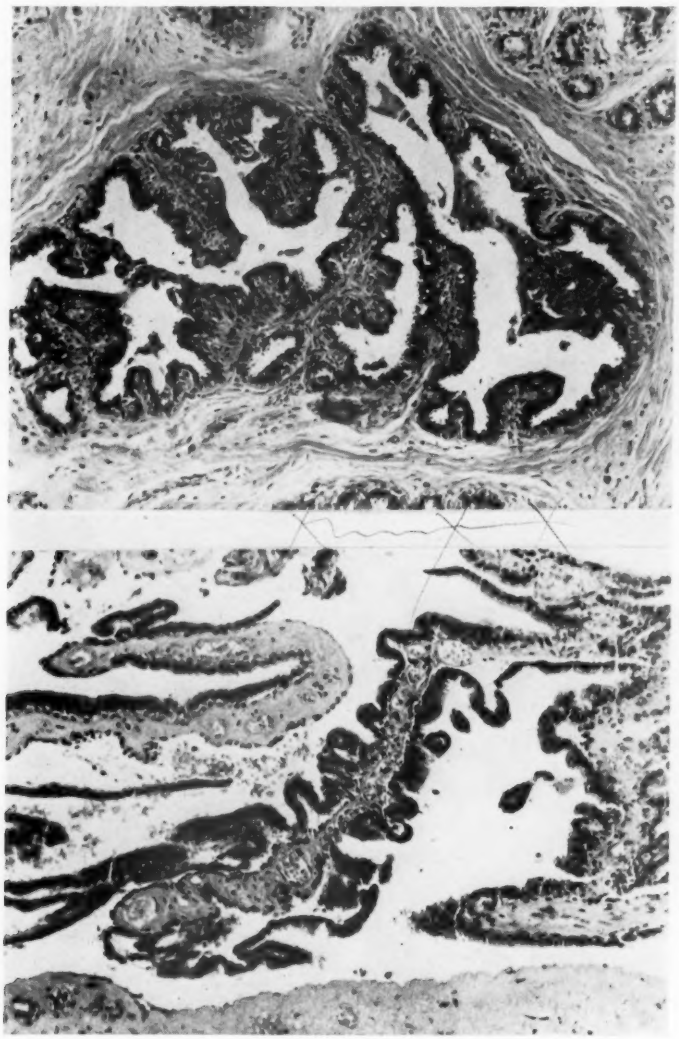


FIG. 2

FIG. 1.—Orderly vascularized papillomatosis of medium-sized mammary ducts. (Figures 1 through 8 are taken from a single breast)
FIG. 2.—Portion of a 1.5-cm. papilloma in a large duct. Orderly structure.

wall. On occasions this myoid element is seen at or near the main stem of a "parent" blunt duct, but it invariably disappears within a space of a millimeter. The elastica in the walls of these ducts is quite variable in amount, but commonly one sees in the breast tissue adjacent, an apparent

condensation of extraductal elastica. The initial branch of a blunt end duct may not divide, but ordinarily one and often many subdivisions are encountered in serial sections. They are apt to end in a cluster of closely but irregularly spaced blind channels but with no resemblance to usual lobule formation. It is to be noted that these structures have long since lost their

FIG. 3

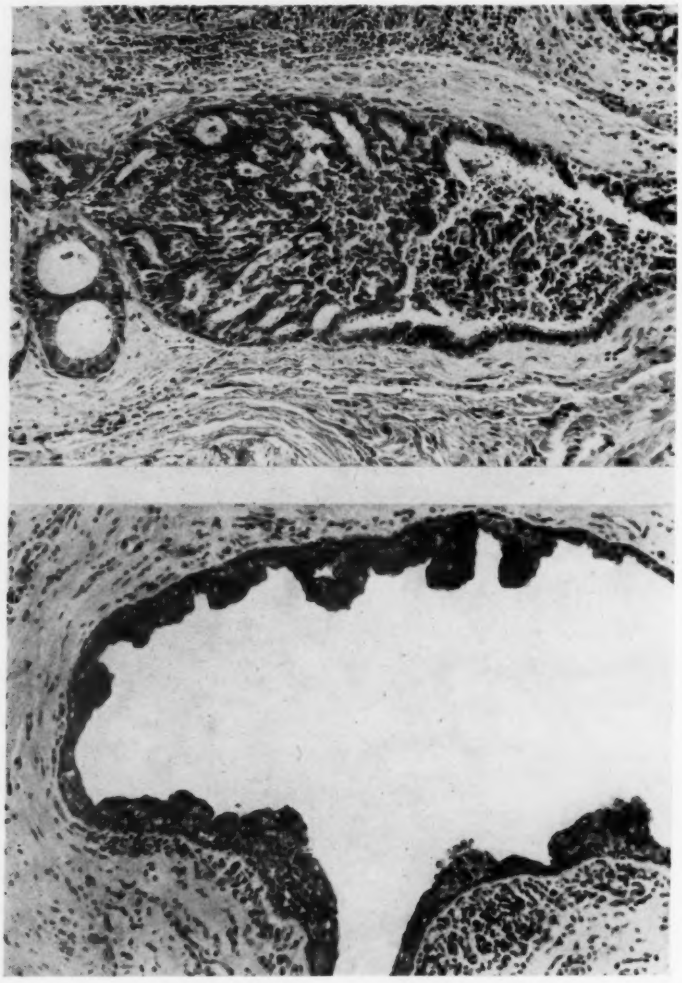


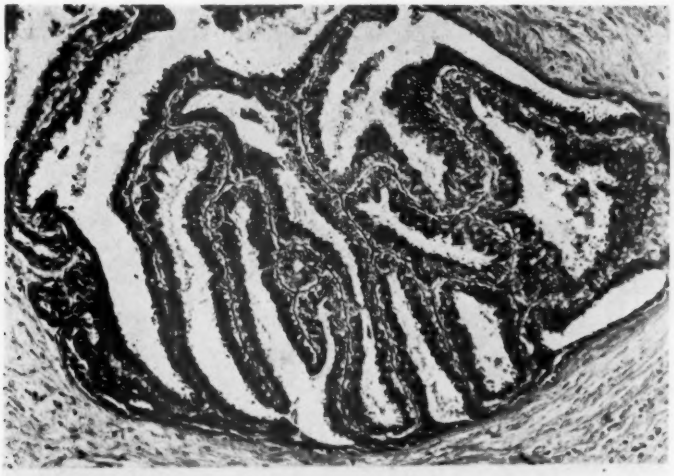
FIG. 4

FIG. 3.—Less orderly papillary and partly solid hyperplasia. Not vascularized.
FIG. 4.—Nonvascular stratification and papillary piling-up. Cytology atypical.

myoid envelope, whereas in the mammary lobules it is common for the terminal duct to retain its myoid layer until or even after it enters the lobule. The blunt end ducts furthermore often have relatively wide lumina which are actually wider by far than the mammary ducts from which they sprouted. The epithelial lining of these ducts is by no means uniform and

is apt to vary from point to point in any given duct or its divisions. Sometimes there is a two-layered epithelial lining with a low or flat basal row and an outer row that varies from low to quite tall cylindrical. Often the inner row of cells extrudes from its distal border a pink, homogeneous "cytoplasmic prolongation" identical with what is often seen protruding from

FIG. 5



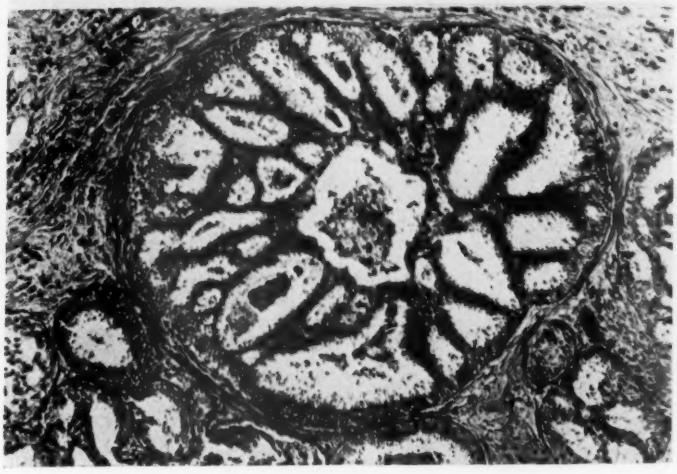


FIG. 6

FIG. 5.—Intraductal papilloma cytologically rather uniform except at left lower corner. Over-all pattern atypical in spite of dominant maintenance of polarity.

FIG. 6.—Distinctly more advanced alteration of same general pattern as Figure 5. Low-grade intraductal papillary carcinoma.

the cells of normal mammary ducts. In addition to the relatively orderly epithelial lining just mentioned all degrees of stratification continuing to papillomatosis appear, and are by no means uncommon. It is not very unusual to find apocrine metaplasia of the epithelial lining of blunt end ducts. Finally,

blunt end ducts may have a single low or flat row of epithelium. The variable structure of blunt end ducts seems in all likelihood referable to whether the process is seen in an early or late phase. The early lesions have relatively narrow lumina with taller lining cells while the later lesions show broader lumina and shorter lining cells. Mitoses are uncommon but far more apt

FIG. 7

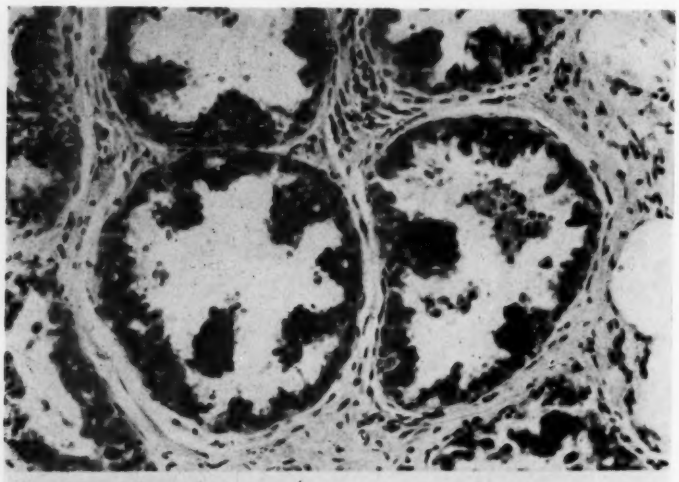


FIG. 8

FIG. 7.—Papillary intraductal carcinoma.
FIG. 8.—Fully developed intraductal and infiltrating carcinoma.

to occur in the earlier proliferative phases. In a single breast, blunt end ducts of every phase may be found, as if the organ had responded to multiple periods of stimulation alternating with periods of quiescence. The very late phases of great dilatation and flattening of epithelium practically never show any sign of proliferation. The degree of blunt duct adenosis ranges

from an occasional focus to a level where almost all of a several centimeter mass of breast tissue may be made up principally of these structures. In such a marked case, two findings stand out. There are practically no lobules, and small- (1–2 Mm.) and medium- (1 cm.) sized cysts are very numerous. This supports the idea of an origin of blunt end ducts from terminal ducts, with subsequent lobule obliteration as the dilatation progressively involves the preexisting lobules. It further suggests that cyst formation may be an end-result of blunt duct adenosis. Finally, the smallest cysts one sees invariably fail to have a circumferential layer of myoid.

In the 200 noncancerous breasts blunt duct adenosis was seen in 52, or 26 per cent, and in the 300 cases of mammary cancer, the figures are 78, or 26 per cent. By decades the occurrence is as shown in Table X.

TABLE X

OCCURRENCE OF BLUNT DUCT ADENOSIS

Decade	Noncancer Cases	Cancer Cases
30–40	36%	28%
40–50	28%	45%
50–60	20%	13%

The divergence in the frequency of blunt duct adenosis in the decade 40–50 is the greatest shown. A possible explanation for this is presented in the following: It has been previously shown in the decade 40–50 that cysts occurred in 65 per cent of noncancerous breasts and in only 18 per cent of cancerous breasts. It also seems, on the basis of preceding morphologic observation, that blunt duct adenosis is apt to eventuate in cyst formation. Hence, one may suggest that for the decade 40–50 the tendency in the benign cases is toward cyst formation with partial obliteration of the structures from which they arose. Consequently, there is a relative diminution of these antecedent structures in the age-period when cysts are most common. Similarly, in the decade 40–50 the tendency in the cancer cases is away from cyst formation, and this results in a greater relative frequency of the antecedent structures in the age-period when cysts are relatively fewest. It is, likewise, apparent that these blunt end ducts become less frequent with advancing age, hence sharing in the general tendency toward atrophy of the mammary system.

Table XI enumerates the lesions that accompany blunt duct adenosis. As in preceding tables, the frequency of these lesions as they occur in the cancer and noncancer groups as a whole is represented.

Quantitative differences again are shown and particularly noticeable is the marked tendency for the previously designated cystic and proliferative lesions to occur simultaneously, namely, cysts, hyperplasia of duct epithelium, duct papillomatosis, blunt duct adenosis, apocrine epithelium and sclerosing adenosis. Emphatically presented, again, is the failure of fibro-adenoma to be accented with this group. No differential feature between cancerous and noncancerous breasts appears that is not explainable by the preliminary comparisons of these types of breasts in various age groups.

TABLE XI

LESIONS ACCOMPANYING BLUNT DUCT ADENOSIS

	52 Noncancer Cases, with Blunt Duct Adenosis	200 Consecutive Noncancer Cases	78 Cancer Cases, with Blunt Duct Adenosis	300 Consecutive Cancer Cases
1. Hyperplasia of duct epithelium	77%	39%	84%	57%
2. Duct papillomatosis	60%	29%	61%	36%
3. Intracystic papilloma	Not charted	2%	Not charted	1%
4. Apocrine epithelium	63%	42%	53%	39%
5. Sclerosing adenosis:				
A. Diffuse	2%	1.5%	1%	0.3%
B. Focal	27%	11%	14%	7%
6. Fibro-adenoma	14%	19%	6.5%	7%
7. Tendency to fibro-adenoma	13%	3%	6.5%	6%
8. Cysts	87%	53%	44%	27%
9. Stasis and distention of ducts	40%	36%	53%	42%
10. Duct metaplasia	50%	34%	74%	45%
11. Periductal mastitis	30%	22%	15%	14%
12. Fat necrosis	0	2%	0	1.3%
13. Lobule frequency:				
Numerous	11%	13%	14%	10%
Average	68%	61%	41%	35%
Few	21%	26%	45%	55%
14. Periductal myoid atrophy	37%	27%	50%	42%

A further means of cross-analysis is afforded by comparing the cancer and noncancer breasts that show blunt duct adenosis with those that do not.

TABLE XII

COMPARATIVE FINDINGS IN BREASTS WITH AND WITHOUT BLUNT DUCT ADENOSIS

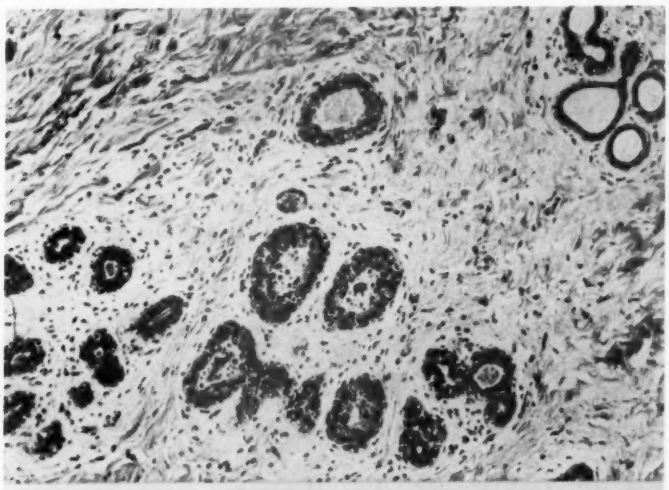
	52 Noncancer Cases, with Blunt Duct Adenosis	148 Noncancer Cases, without Blunt Duct Adenosis	78 Cancer Cases, with Blunt Duct Adenosis	222 Cancer Cases, without Blunt Duct Adenosis
1. Hyperplasia of duct epithelium	77%	25%	84%	47%
2. Duct papillomatosis	60%	18%	61%	28%
3. Intracystic papilloma	Not charted		Not charted	
4. Apocrine epithelium	63%	34%	53%	34%
5. Sclerosing adenosis:				
A. Diffuse	2%	1.5%	1%	0.5%
B. Focal	27%	7%	14%	4%
6. Fibro-adenoma	14%	21%	6.5%	9%
7. Tendency to fibro-adenoma	13%	2%	6.5%	5%
8. Cysts	87%	41%	44%	21%
9. Stasis and distention of ducts	40%	33%	53%	40%
10. Duct metaplasia	50%	30%	74%	36%
11. Periductal mastitis	30%	18%	15%	14%
12. Fat necrosis	0	3%	0	2%
13. Lobule frequency:				
Numerous	11%	13%	14%	9%
Average	68%	57%	41%	33%
Few	21%	30%	45%	58%
14. Atrophy of periductal myoid	37%	24%	50%	39%

The same trends seen in Table XII are repeated in sharper contrast with the accent still on the simultaneous occurrence of the lesions already designated.

Blunt duct adenosis cannot be associated with pregnancy or nursing, inasmuch, as these states were equally common in the cases with or without this lesion and, further, blunt duct adenosis is seen in individuals who have

never been pregnant. Finally, these structures show no relation to the phasic changes of the menstrual cycle. They are, undoubtedly, proliferative manifestations and they apparently can exist for considerable periods, eventuate in cyst formation, or undergo involution and atrophy.

FIG. 9



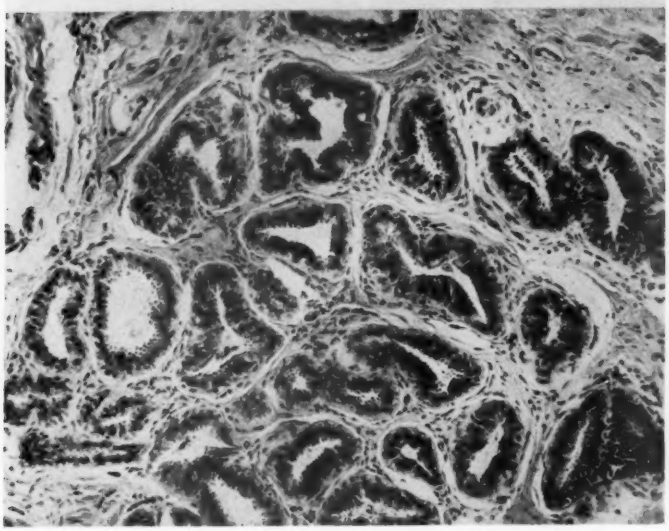


FIG. 10

FIG. 9.—Relatively early phase of blunt duct adenosis. Failure of normal lobule formation.

FIG. 10.—Process of blunt duct adenosis more fully developed.

It is difficult to be sure of the part blunt end ducts play in the morphogenesis of mammary carcinoma. Papillomatosis occurs in blunt end ducts but it is not as common as in the permanent duct system and is far less liable to show histologic atypism. Any duct that is the site of papillomatosis is very

likely to show atrophy of its periductal myoid layer and, since absence of myoid is a prime characteristic of blunt end ducts, there are many occasions when one is uncertain whether to call a papilloma-containing duct a permanent duct or a newly formed blunt end duct. We were able to trace cancer to

FIG. 11

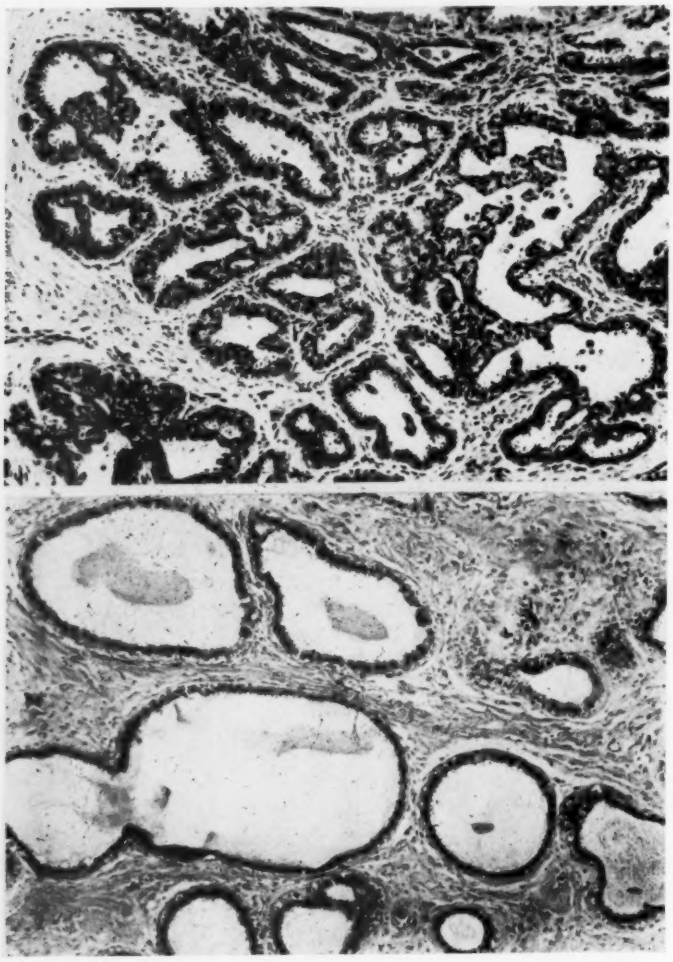


FIG. 12

FIG. 11.—Papillomatosis in a group of blunt end ducts.
FIG. 12.—Intermediate phase of blunt duct adenosis. Subsidence of proliferative impulse, widening of lumina.

this source with reasonable certainty in only four out of 300 cases, which is in all probability a somewhat low figure. Some of the principal structural traits of blunt duct adenosis are represented in Figures 9 through 13.

V. APOCRINE EPITHELIUM

This term refers to epithelium consisting of the very characteristic large, usually tall, cylindrical cells that have relatively small nuclei and abundant,

clear, bright, eosinophilic cytoplasm. Aggregates of this kind of epithelium can commonly be seen in the gross as discrete yellowish-brown, slightly elevated, glistening areas, usually 1–2 Mm. in diameter but occasionally of much larger dimension. The larger aggregates are almost invariably partly cystic

FIG. 13

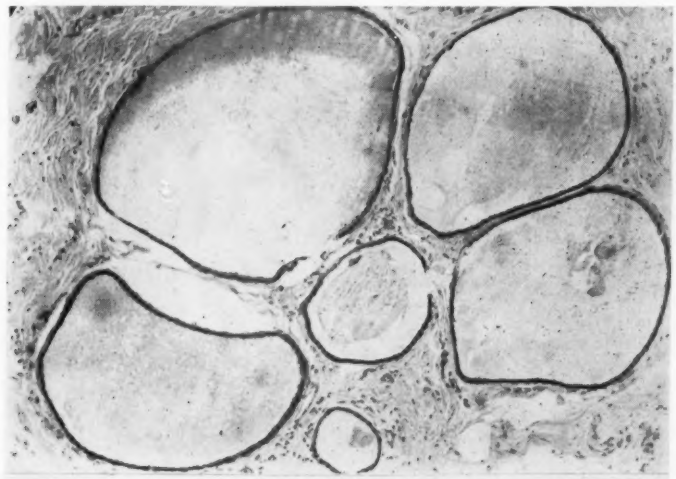


FIG. 14

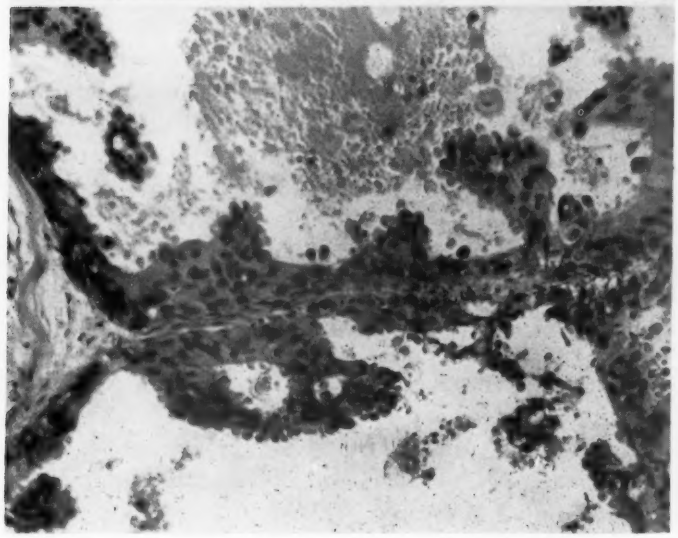


FIG. 13.—Late phase of blunt duct adenosis.
FIG. 14.—Apocrine epithelium in papillary form. Cytology not atypical.
(Figures 14 through 17 were taken from a single breast)

and/or adenomatoid. Microscopically, in single sections, apocrine epithelial islands may be seen as apparently isolated glandular or cystic structures or, less often, they are seen in direct continuity with a mammary duct that is lined elsewhere by conventional epithelium. When examined in serial

sections, it is surprising how often a connection with ducts or lobules is demonstrated, and it becomes evident that this is the usual structural relationship. Complete isolation from the duct system is shown on occasion and, when this is true, cystic distention is the rule. Papillary hyperplasia of slight or moderate degree is rather common, appearing in about a third of apocrine epithelial foci of both cancerous and noncancerous breasts.

Some form of apocrine epithelium was seen in 42 per cent of breasts free from cancer, and in 39 per cent of breasts containing cancer. Most of these findings are based on microscopic study and, hence, are largely chance observations. The frequency would of course be greater if very numerous blocks were made, and we can only regard the figures given here as comparative and not absolute. Table XIII shows the incidence by decades.

TABLE XIII

OCCURRENCE OF APOCRINE EPITHELIUM

Decade	Noncancer Cases	Cancer Cases
30–40	33%	25%
40–50	47%	44%
50–60	40%	31%

Thus, no wide divergence can be demonstrated between cancer and noncancer cases. It is worth noting, however, that these structures are most frequent during the decade 40–50, when the breast shows its highest level of noncancerous proliferative lesions. Without the series of noncancerous breasts as a control group, the common occurrence of this kind of epithelium in cancer cases might be interpreted as being important in mammary cancerigenesis, especially by those who claim that a high proportion of breast cancers are of sweat gland origin, which viewpoint we emphatically reject. The same is equally true of other lesions, but it is our desire to show that mere statistical association needs the support of demonstrable morphologic relationship before any given lesion can be ascribed a place of importance in the actual histogenesis of cancer. Pursuing this course as regards apocrine epithelium, it was possible to designate only three mammary cancers in 300 as showing histologic characters that would prove or suggest origin from this source. Furthermore, it is difficult to find in either cancerous or noncancerous breasts any foci of apocrine epithelium that show histologic atypism. In the 500 cases studied here, only two examples of this change were found. Both of these atypical foci were papillary and in each case the breast contained a cancer. One of these was an infiltrating duct carcinoma of usual type and the other a carcinoma with quite large cylindrical cells having relatively small nuclei and abundant clear, eosinophilic cytoplasm. In a large series of mammary cancers about 3 per cent are composed of cells resembling the apocrine type. There is then no way of ascribing a major morphologic rôle to these cells in mammary carcinogenesis. It is not possible to detect transitions from mammary apocrine epithelium to mammary cancer in any but the very exceptional case. Such a sequence is shown in Figures

FIG. 15

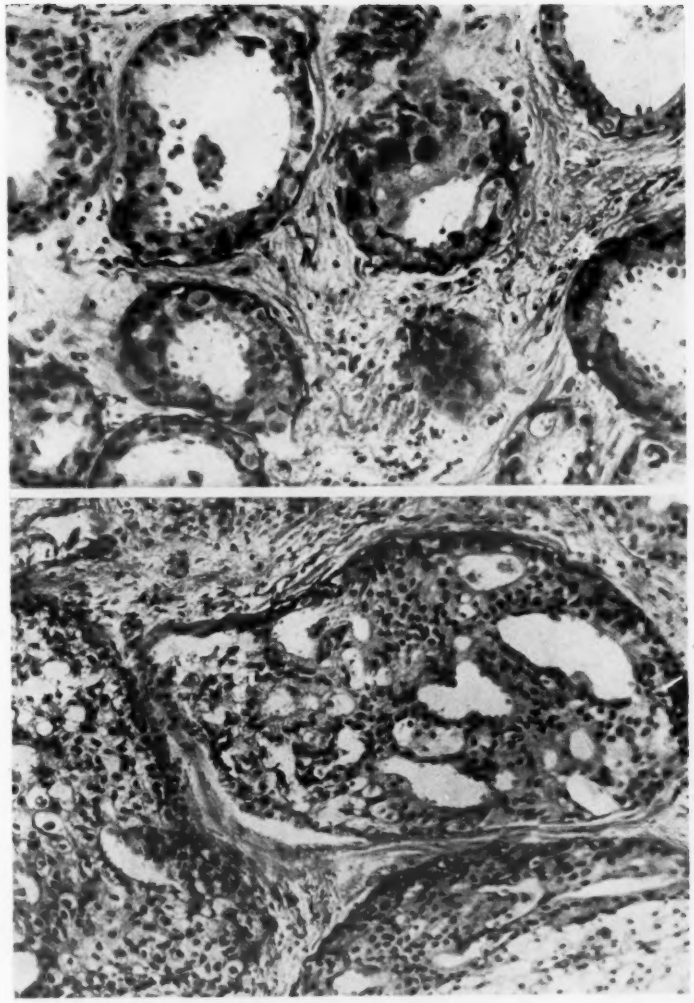


FIG. 16

FIG. 15.—Ducts lined by apocrine epithelium, portions of which are of atypical structure.

FIG. 16.—Noninfiltrating carcinoma composed of apocrine epithelium.

FIG. 17

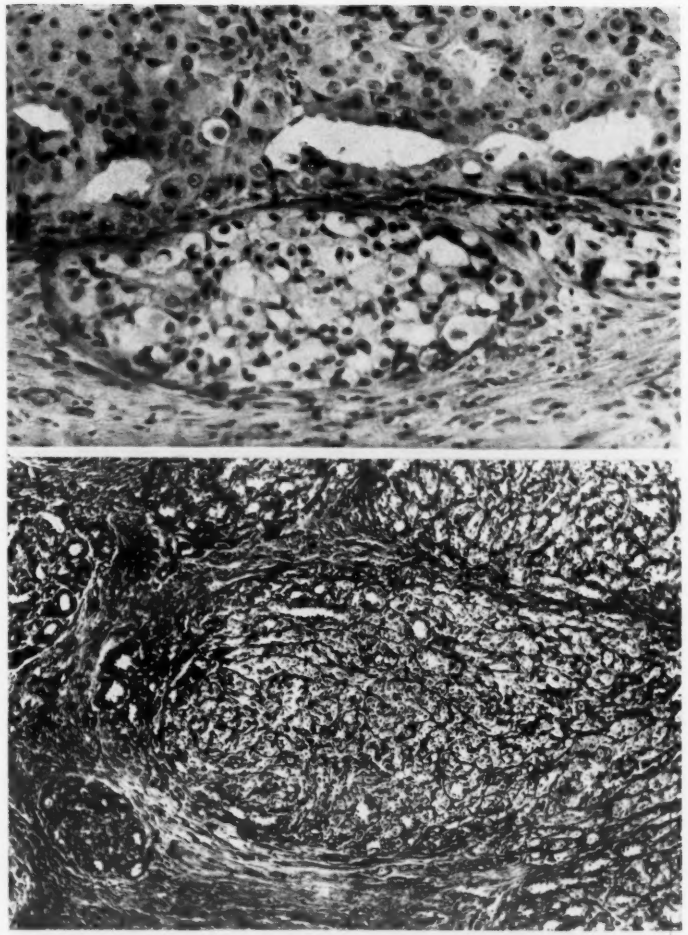


FIG. 18

FIG. 17.—Intraductal and infiltrating carcinoma made up of apocrine cells.

FIG. 18.—Highly cellular, florid phase of sclerosing adenosis. Single field of type commonly confused with mammary carcinoma. Section from a discrete 2.5 cm. mass.

14 through 17, the illustrations being taken from a single breast. All the epithelium shown had the characteristic eosinophilic tinctorial quality. Axillary nodes were involved in this case.

Table XIV is designed to show what lesions are apt to occur in cancerous and noncancerous breasts when the common factor is the presence of apocrine epithelium. As usual, the occurrence of these lesions in the 200 benign breasts and 300 cancerous breasts, as a whole, is included.

TABLE XIV

LESIONS ACCOMPANYING APOCRINE EPITHELIUM

	84 Noncancer Cases, with Apocrine Epithelium	200 Noncancer Cases	117 Cancer Cases, with Apocrine Epithelium	300 Cancer Cases
1. Hyperplasia of duct epithelium	65%	39%	70%	57%
2. Duct papillomatosis	45%	29%	45%	36%
3. Intracystic papilloma	0	2%	1%	1%
4. Blunt duct adenosis	56%	26%	47%	26%
5. Sclerosing adenosis:				
A. Diffuse	1%	1.5%	0	0.3%
B. Focal	23%	11%	14%	7%
6. Fibro-adenoma	8%	19%	6%	7%
7. Tendency to fibro-adenoma	4%	3%	8%	6%
8. Cysts	83%	53%	40%	27%
9. Stasis and distention of ducts	50%	36%	62%	42%
10. Duct metaplasia	52%	34%	71%	45%
11. Periductal mastitis	30%	22%	20%	14%
12. Fat necrosis	0	2%	2%	1.3%
13. Lobule frequency:				
Numerous	10%	13%	7%	10%
Average	59%	61%	39%	35%
Few	31%	26%	54%	55%
14. Periductal myoid atrophy	37%	27%	45%	42%

TABLE XV

COMPARATIVE FINDINGS IN BREASTS WITH AND WITHOUT APOCRINE EPITHELIUM

	84 Noncancer Cases, with Apocrine Epithelium	116 Noncancer Cases, without Apocrine Epithelium	117 Cancer Cases, with Apocrine Epithelium	183 Cancer Cases, without Apocrine Epithelium
1. Hyperplasia of duct epithelium	65%	19%	70%	42%
2. Duct papillomatosis	45%	24%	45%	30%
3. Intracystic papilloma	0	3%	1%	2%
4. Blunt duct adenosis	56%	4%	47%	12%
5. Sclerosing adenosis:				
A. Diffuse	1%	2%	0	2%
B. Focal	23%	5%	14%	2%
6. Fibro-adenoma	8%	27%	6%	8%
7. Tendency to fibro-adenoma	4%	6%	8%	4%
8. Cysts	83%	31%	40%	19%
9. Stasis and distention of ducts	50%	25%	62%	30%
10. Duct metaplasia	52%	22%	71%	30%
11. Periductal mastitis	30%	16%	20%	11%
12. Fat necrosis	0	3%	2%	1%
13. Lobule frequency:				
Numerous	10%	14%	7%	13%
Average	59%	59%	39%	32%
Few	31%	27%	54%	55%
14. Periductal myoid atrophy	37%	20%	45%	39%

The trends shown in previous tables are repeated in Table XIV, and in Table XV a further comparison is shown by charting the lesions occurring in breasts that do and do not contain apocrine epithelium.

Study of the preceding tables justifies the statement that apocrine epithelium is most apt to be found in a breast containing certain noncancerous proliferative lesions. This is further supported by the following: Rather commonly in cases of papillomatosis, isolated foci of apocrine cells or glands are seen in that part of the papilloma which protrudes into the duct lumen. These foci are often multiple and are entirely separated from one another, so that it seems reasonable under these circumstances to regard them as metaplastic in nature, newly formed, and, therefore, proliferative. It can also be shown that apocrine elements take part in sclerosing adenosis and blunt duct adenosis, the component parts of which are certainly newly formed structures. Occasional mitoses may be found in areas of epithelium of apocrine pattern, indicating that these are in some instances at least proliferative rather than static structures. We believe that all "pink epithelium" in the breast arises on a basis of hyperplasia and metaplasia. Absolute determination of this would depend on studying material from breasts of gradually decreasing age-groups until the earliest manifestations are encountered. We have seen apocrine elements in a breast of an infant a few months old. This was, however, in an actively proliferative adenomatoid lesion of papillary character.

In summary, an analysis of cancerous and noncancerous breasts, using the presence or absence of apocrine epithelium as the means of comparison, shows no essential difference.

VI. SCLEROSING ADENOSIS

The terms "fibrosing adenomatosis," "sclerosing adenomatosis" and "sclerosing adenosis" have long been used interchangeably in this Hospital to identify a specific lesion quite commonly misinterpreted and erroneously diagnosed as mammary carcinoma. The interchangeable terms above are incompletely descriptive since they designate only one phase of the process to be described here, namely, that of sclerosis. These lesions have been also termed "myo-epithelial" tumors.[1] The phase of fibrous sclerosis, however, is the one usually seen, it is quite characteristic, and hence it seems permissible to stress this feature in selecting a term applicable to the lesion. The stage of fibrous sclerosis is, of course, a late one and it is not usual to see the earlier or "florid" phase of pure epithelial efflorescence. So far, we have seen only a single case in which the microscopic structure was purely "florid." It is rare to find "floridness" the chief feature in any case, but over a period of some years all conceivable intermixtures of florid areas and sclerosing areas have been observed.

Sclerosing adenosis occurs in two forms. In the first of these a palpable tumor mass is present. In the second, minute focal areas are seen only on microscopic examination and the lesions are but incidental findings. The

focal microscopic lesions are 20 to 30 times as frequent as the discrete tumors, and present no clinical problem.

When sclerosing adenosis presents as a palpable lump the true identity of the process can be established by the following characters: The lump is freely movable in the breast and there are no secondary skin changes. The patients are usually in the twenties or thirties. We have seen no case below puberty and only a few in the teens. Now and then the lesion occurs after forty and in isolated instances in the fifties and sixties. The tumors are customarily seen by the pathologist when a specimen is locally excised and submitted for frozen-section, the clinical diagnosis having been fibro-adenoma or cyst. The consistency is ordinarily less rubbery than in fibro-adenoma and less firm than in mammary carcinoma. However, both extremes are possible. The tumors lack the smooth globoid or elliptical shape of a fibro-adenoma and instead show nodularity of varying coarseness. They are discrete but are apt to be indefinitely encapsulated. On section, resistance to cutting is variable, depending on elasticity or firmness. The cut surface is grayish-white as a rule but may be partly or chiefly faint, pinkish-yellow. Usually, the chalky streaks so common in mammary cancer are absent but in several instances they have been observed. The most important gross observation is the detection of usually definite lobulation that may vary from a millimeter to over a centimeter. The lobulations are chiefly in direct contiguity but they may merge imperceptibly or sometimes be separated by an interval of a few millimeters. There is often a certain minor degree of translucence. The lobulated surfaces customarily project slightly. The periphery of the tumor is characteristically noninfiltrating in appearance but some specimens may be confusing in this respect. Given a case in which there is distinct lobulation, neat circumscription and an absence of chalk streaks, a gross diagnosis of cancer is unlikely. But there are a few cases in which lobulation and circumscription are not clear and if chalk streaks and undue firmness are added, one is very apt to get a gross impression of mammary cancer. Fortunately, this combination of characters is rare. If the gross impression of cancer is carried over to the frozen or paraffin section, danger is increased since further microscopic confusion is possible.

The chief pitfall in microscopic diagnosis, particularly in frozen sections, is seeing what superficially appears to be infiltration. When properly analyzed, it becomes evident that this picture is the result of abortive fibrosis or hyalinosis. It is the stage of sclerosis where epithelium has lost the initiative and is "choked" by fibrous or hyaline matrix. This connective tissue dominance produces irregular patterns where thin epithelial columns are haphazardly isolated. Due to constrictive pressure the shape of the epithelial cells is apt to be variable, and the sum total yields an impression of pleomorphism plus invasiveness. It is important to note that, at this phase of the process, nuclear staining is regular and mitoses are absent. Looked at with a low power lens one is often able to detect lobulation even when it is

grossly inconspicuous, and it is usual to find that the greatest degree of sclerosis occurs at the periphery of the lobulated portions. Eventually the entire area of lobulation will become hyalinized, but this is a change that may require many years. In almost any case certain microscopic fields can be found which, if viewed alone, would certainly pass for cancer, and

FIG. 19

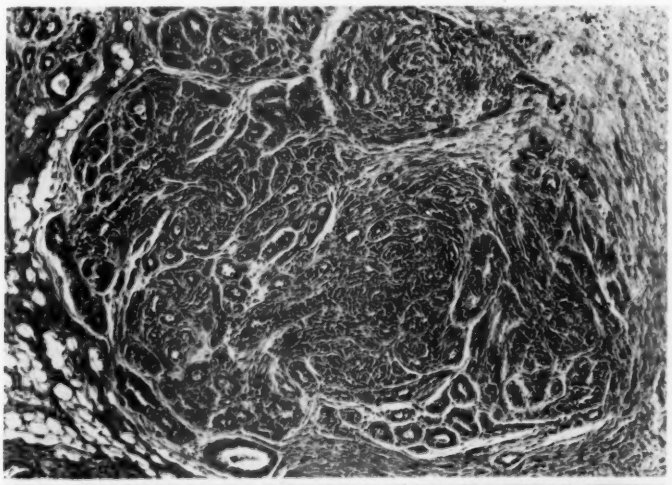


FIG. 20

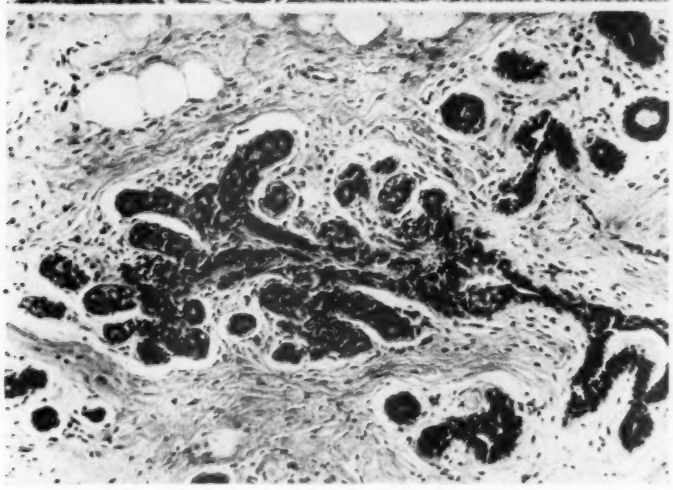


FIG. 19.—Section from a palpable mass. Intermediate phase with moderate sclerosis.

FIG. 20.—Focal lobular area of sclerosing adenosis. No palpable mass. Beginning sclerosis.

it is necessary that the lesion be examined as a whole and the various changes reconstructed, to insure proper interpretation. The occurrence of cellular areas in these tumors is a further source of microscopic confusion. It has been stated before that florid and sclerosing areas may be present in the same tumor.

During the florid phase moderate cellular variability may be seen and mitoses are not infrequent. These findings must also be discounted and the decision as to diagnosis made on estimating all of the features present. During the florid phase there is extensive multiplication of duct-like structures. Both extra- and intralobular members of the mammary paren-

FIG. 21

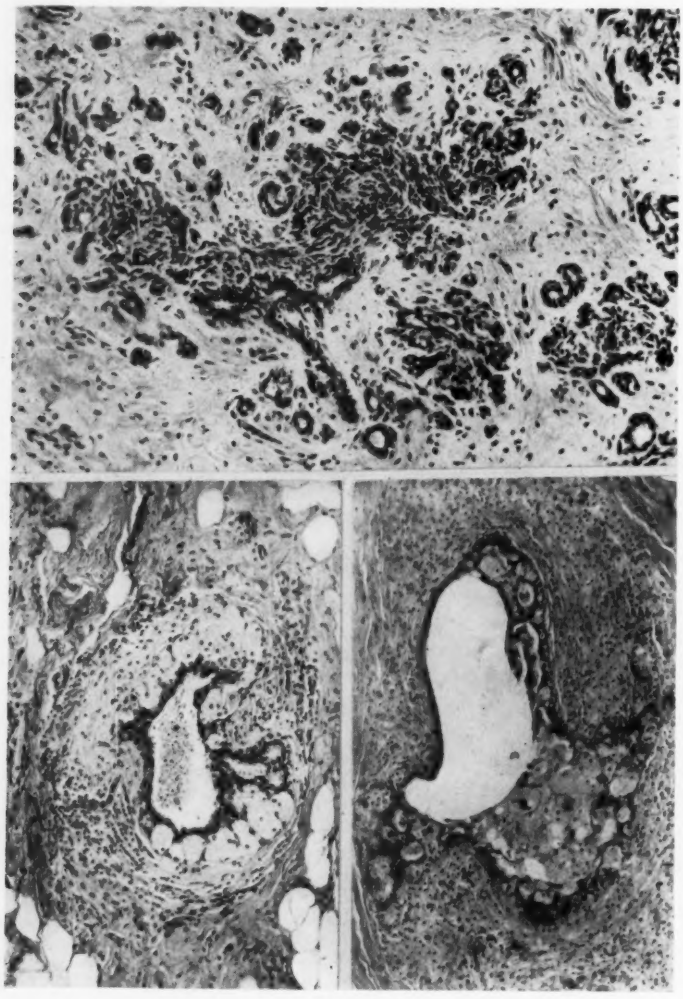


FIG. 22 FIG. 23

FIG. 21.—Advanced stage of sclerosing adenosis with obliteration of lumina. No palpable mass.

FIG. 22.—Dilated mammary duct containing stasis material. Periductal inflammation with infiltrate of lymphocytes and large fat-filled phagocytes.

FIG. 23.—Same process as in Figure 22, but somewhat more advanced.

chyma are seen to participate and the newly formed ducts often show papillary and solid epithelial plugging. Sometimes the proliferation is so diffuse that solid epithelial islands, small and large, are formed in which lumina are not visible, and again single microscopic fields can be found

that would be individually indistinguishable from cancer. In purely florid areas connective tissue does not participate. Even in the florid phase of sclerosing adenosis there is a tendency to lobulation. A generalization may be made that in either phase, the lesion is "put together" in a different fashion than is mammary cancer. Some of the microscopic qualities of sclerosing adenosis are reproduced in Figures 18 through 21.

It seems clear enough that sclerosing adenosis can begin in an intralobular position or commence in near-terminal or terminal ducts that fail to form normal mammary lobules. This view of origin is supported by the fact that the newly formed tubular structures practically never have a circumferential myoid investment. When sclerosing adenosis presents as a palpable mass, lobule participation in the tumor proper may not be visible but in outlying breast tissue it is commonly observed. In the focal microscopic form of sclerosing adenosis lobular origin is by far the more common, and often the lesions are of such small proportion that normal lobule size may be maintained, and in some lobules all of the lobule constituents do not necessarily participate. Both florid and sclerosing phases can be seen in the focal microscopic form of sclerosing adenosis, and the only real difference between this form and the tumorous form is that one occurs in miniature.

It may be well to repeat that sclerosing adenosis infrequently produces a palpable tumor. This infrequence is undoubtedly the chief reason that it is so apt to be mistaken for cancer. On a Surgical Service that does over a thousand breast operations yearly, the annual occurrence of the palpable or clinical form of the disease ranges from six to twelve cases.

In the 200 noncancerous cases studied here, three discrete tumors due to sclerosing adenosis were seen, while in the 300 cancer cases, there was only one example, in addition of course, to the cancer. In the statistics to follow, these few instances of discrete tumor cases have been merged with the focal microscopic type. Thus, in 200 breasts without cancer, sclerosing adenosis was found in 12.5 per cent and in 300 breasts containing cancer, in 7 per cent. The number of cases in either group is insufficient to give reliable percentage figures by decades, but this is nevertheless shown in Table XVI.

TABLE XVI

INCIDENCE OF SCLEROSING ADENOSIS

Decade	Number of Noncancer Cases, with Sclerosing Adenosis	Number of Cancer Cases, with Sclerosing Adenosis
20–30	5	0
30–40	4	2
40–50	16	9
50–60	0	3
60–70	0	6

The only impressions that can be gained from Table XVI are that sclerosing adenosis (in essence, the focal microscopic form) is most common in the decade 40–50, and that the lesion, as such, can endure in the breast far beyond the menopause.

Table XVII shows the lesions that occur together with sclerosing adenosis.

TABLE XVII

LESIONS ACCOMPANYING SCLEROSING ADENOSIS

	26 Noncancer Cases, with Sclerosing Adenosis	200 Noncancer Cases	20 Cancer Cases, with Sclerosing Adenosis	300 Cancer Cases
1. Hyperplasia of duct epithelium	60%	39%	85%	57%
2. Duct papillomatosis	56%	29%	75%	36%
3. Intracystic papilloma	0%	2%	0%	1%
4. Blunt duct adenosis	60%	26%	60%	26%
5. Apocrine epithelium	52%	42%	70%	39%
6. Fibro-adenoma	16%	19%	5%	6%
7. Tendency to fibro-adenoma	4%	3%	5%	6%
8. Cysts	64%	53%	60%	27%
9. Stasis and distention of ducts	32%	36%	65%	42%
10. Duct metaplasia	44%	34%	75%	45%
11. Periductal mastitis	26%	22%	20%	14%
12. Fat necrosis	0%	2%	0%	1.3%
13. Lobule frequency:				
Numerous	28%	13%	10%	10%
Average	52%	61%	45%	35%
Few	20%	26%	45%	55%
14. Periductal myoid atrophy	36%	27%	55%	42%

From the foregoing it is clear that other cystic and proliferative lesions of types previously mentioned, tend to occur along with sclerosing adenosis; and, moreover, they occur with greater than usual frequency. One proliferative lesion, fibro-adenoma, does not follow this trend nor has it done so in former analyses.

It does not seem possible to show a fundamental difference between cancerous and noncancerous breasts on the basis of sclerosing adenosis. That this lesion has little or no part to play in mammary cancerigenesis we now feel reasonably certain. We have never seen any crucial morphologic evidence in any case that a mammary carcinoma was arising on a basis of sclerosing adenosis. The very occasional case in which cancer and sclerosing adenosis merge in the same microscopic field has always shown more convincing evidence of origin from other sources or simultaneously in sclerosing adenosis and other sources, so that satisfactory traceability to sclerosing adenosis as a precancerous entity has been lacking and the coexistence attributed to chance. For years, conservative local surgery has been recommended in cases of sclerosing adenosis, and no incident yet has occurred to alter this point of view.

The etiology of this lesion is unknown. The microscopic appearance does not change with phases of the menstrual cycle. Menstrual histories of the patients reveal nothing characteristic. In one case the patient, age 24, presented a 1.5-cm. lump in her breast that had been present and unchanged for six months. A 20 mg. pellet of estradiol was implanted adjacent to the lump. During 12 weeks of observation the lump in her breast changed not at all in character. At the end of this period the pellet and the breast tumor with adjacent breast tissue were excised. At the time of removal

the pellet weighed 14 mg. The 1.5-cm. mass was a fibro-adenoma, with focal areas of sclerosing adenosis. In the adjacent breast tissue were additional foci of sclerosing adenosis. All areas of sclerosing adenosis were similar in structure and in the phase of fibrous sclerosis. None of the usual features of the florid phase was seen. This case was of interest because of the apparent negative response of the sclerosing adenosis (and for that matter the surrounding breast tissue) to estradiol administration.

Highly florid focal sclerosing adenosis has been observed in the breast of one pregnant patient. However, comparison with florid lesions in breasts of nonpregnant individuals renders it impossible to state that the concomitant pregnancy increased the floridity of the lesion, since equal degrees of floridity occur quite apart from pregnancy. Every phase of the process has been seen in individuals who have never been pregnant, from which it is obvious that pregnancy is not a necessary initiating growth factor, and it is not a postlactational involutional phenomenon. Material studied to date has given no clue to what initiates the early or florid phase. It can be said that this pattern is much more common in the third and fourth decades, but on occasion unusually florid cases are seen in older women, an extreme example being in a patient age 62. The period during which a lesion may remain in a florid phase is also indeterminate but this character was seen in one tumor whose presence had been known for 12 years. In another florid case, the lump was first noted shortly after injections of unstated amounts of theelin. In still another case the lump was observed prior to theelin therapy, and after administration of 100,000 units, the symptoms of lump were said to have been partially relieved. In the section, however, the histology was anything but that of a lesion presumably "relieved," the florid characters being extremely prominent. These chance observations cannot, of course, answer questions on etiology, but they tend to emphasize the unpredictability of hormonal influences.

VII — PERIDUCTAL MASTITIS

The most common histologic feature of periductal mastitis is more or less inflammatory cell infiltrate about the mammary ducts, the predominant cells usually being lymphocytes. The appearance of inflammatory cells, however, is in nearly every case preceded by other changes, namely, stasis of amorphous acellular and cellular duct content, dilatation of the duct wall and varying degrees of atrophy of periductal myoid tissue. A common accompaniment of the process is flattening of the lining epithelium of the duct, usually slight, but in severe cases quite marked so that true squamous metaplasia results. Also, commonly observed are fat-laden phagocytes within the duct lumen, scattered or clustered among the lining epithelial cells and/or dispersed about the duct wall in varying numbers where they mingle with other cells, usually lymphocytes. If the lining epithelium and wall of a duct are eroded, it is not uncommon to find old or fresh blood in the lumen or adjacent periductal tissue, and this is responsible for some cases that

present clinically with bleeding nipple as the chief symptom. Every conceivable combination and degree of these changes are observed, but over-all the most constant finding is stasis of duct content. The cause of stasis is not apparent, but it is reasonably certain that anatomic obstruction to ducts is not essential. No doubt obstruction due to duct papillomas, pressure from cysts or tumors or senile atrophy with duct dilatation facilitate the process, but on close analysis these factors do not explain many of the cases. When these lesions seem concerned the periductal mastitis occurs distally. Such lesions seldom account for the most marked or extensive cases. In noncancerous papillomatosis of multiple small ducts, there is seldom associated periductal mastitis when the papillary lesions are early and small. A solitary macroscopic papilloma is far more apt to prôduce this lesion and the changes appear to depend on the production of stasis of duct content. Furthermore, in comedocarcinoma, where the ducts are lined by cancer cells and there is much central necrosis, somewhat analogous to ordinary duct stasis, periductal mastitis is common and apt to be severe.

One of the consequences of duct stasis is erosion of the epithelial lining. This commonly occurs with relatively little inflammatory reaction. When, however, the duct wall is weakened or penetrated the contents of the duct gain access to adjacent tissue and further changes ensue. If the duct is surrounded by dense fibrous tissue, the reaction produced is relatively mild and not extensive. But if the adjacent tissue is fatty, the outpouring of duct content is followed by a more severe and more complicated inflammatory reaction characterized by fat necrosis in which the break-down products of the fat tissue play an aggravating rôle. The end-result is the production of foreign body type of inflammation. Cholesterol, its esters, and fatty acids are found in these areas of inflammation and are easily identified as crystals or by special staining. The process can be extremely chronic, lasting for months and years. In fully developed form, a palpable mass may be produced and the breast present brawny induration. Secondary changes in the overlying skin sometimes occur, and it is readily understandable why on occasion a clinical diagnosis of cancer is made. This clinical condition has been described by Lee and Adair[2] under the designation "traumatic fat necrosis." It is notable, however, that many cases do not give a history of trauma, and when this is lacking the term "inflammatory necrosis" is a better one. Trauma is not an essential by any means to mammary fat necrosis, but one might postulate that trauma to a breast already the seat of stasis, distention and periductal mastitis augments the chances of that breast developing clinical fat necrosis. In summary, we regard periductal mastitis as representing only a part of a pathologic complex, usually preceded by duct stasis and impairment of the duct wall and followed in some instances by varying degrees of mammary fat necrosis. In this connection see Figures 22 through 25.

Periductal mastitis was found in 44, or 22 per cent, of the 200 noncancerous breasts and in 44, or 15 per cent, of the 300 cancerous breasts.

In the 44 noncancerous breasts with periductal mastitis, the average age of the patients was 41.7 years, while in the 44 cases of cancer with periductal mastitis the average age was 49.7. The occurrence by decades is shown in Table XVIII. On account of the morphologic relationship between

FIG. 24

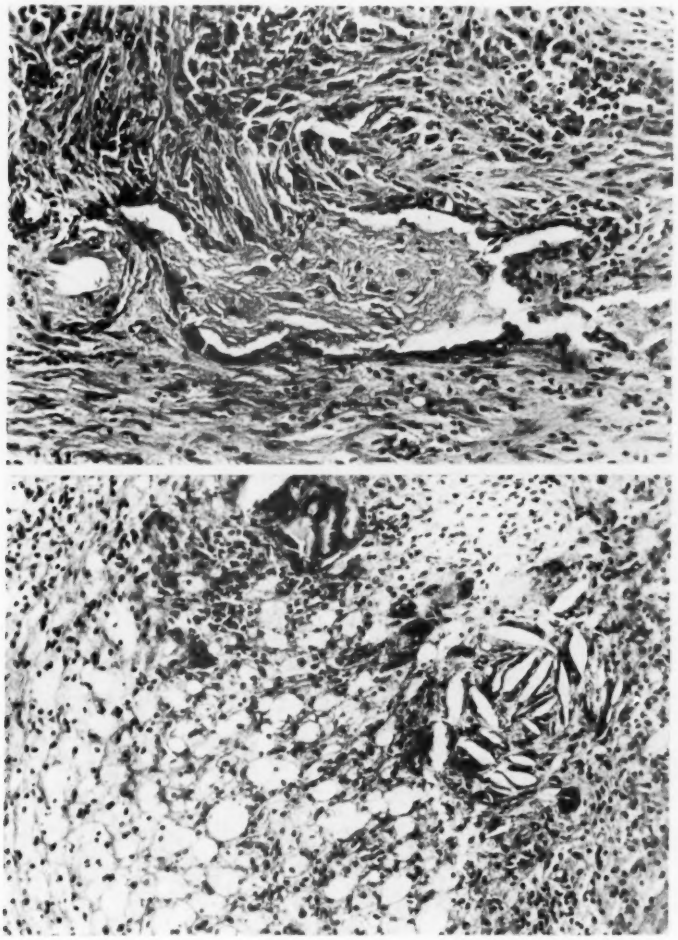


FIG. 25

FIG. 24.—Erosion of lining epithelium and duct wall. Escape of duct content and productive inflammatory response with foreign body characters.
FIG. 25.—Sequela of leakage of duct content; fully developed inflammatory fat necrosis. Spindle-shaped spaces mark former sites of crystalline material removed by solvent chemicals. Many foreign body giant cells.

periductal mastitis and combined stasis and distention of mammary ducts, figures for the latter are included.

The greater frequency of periductal mastitis in breasts without cancer is correlated in each age-group by a correspondingly greater frequency of stasis of duct content and duct dilatation. This statistical interrelationship would not be given so much weight if it were not for the fact that it is

TABLE XVIII

OCCURRENCE OF PERIDUCTAL MASTITIS, STASIS OF DUCT CONTENT AND DUCT DISTENTION

	Noncancerous Cases		Cancer Cases	
Decade	Periductal Mastitis	Combined Stasis and Distention	Periductal Mastitis	Combined Stasis and Distention
30–40	30%	40%	10%	28%
40–50	15%	48%	8%	30%
50–60	48%	70%	18%	48%

supported by morphologic relationship, the simultaneous occurrence of the lesions in the same microscopic or larger areas. Again, it is repeated as in former sections that statistical relations are insufficient for conclusions unless given meaning by concomitant anatomic correlation.

On close examination of periductal mastitis in both groups of cases, it is evident in each that most of these lesions are of slight extent, so that only 22 per cent of the noncancerous breasts with periductal mastitis and 18 per cent of the cancerous breasts with periductal mastitis show the lesion to marked degree. It is of interest that in the entire group of noncancerous cases with periductal mastitis, fat necrosis occurred six times and in every instance the periductal mastitis, stasis and distention were marked. (Note that three of these cases of fat necrosis were from the additional cases added to the 50- to 60-year decade, and, hence, the total of six exceeds the number of cases of fat necrosis in the series of 200 noncancerous breasts). The same was noted in the cancer cases with periductal mastitis. In this group fat necrosis was found four times, always with marked degree of periductal mastitis; stasis and distention, and these cases constituted all examples of fat necrosis in the 300 cases of the cancer series.

Periductal mastitis in both the cancer and noncancer series, as previously mentioned, occurs chiefly with no demonstrable basis except stasis of duct content and dilatation. In the older age-groups this is apt to be rather diffuse (this seems related to the changes of senile atrophy) but may be predominantly focal. In younger women there is a greater tendency to focal distribution. In many cases the periductal mastitis is dependent upon local lesions such as duct papilloma and pressure from cyst or tumor. Thus we regard periductal mastitis in some cases as nonobstructive or "primary" and in some cases as obstructive or "secondary."

The cause for excessive stasis in the primary cases is not clear. The material apparently is composed of desquamative epithelial débris and it may be added to by products of secretion from or through lobular and duct epithelium. Perhaps these changes are due to excessive desquamation or secretion which exceeds the physiologic capacity of the mechanism normally disposing of duct content. Some of the marked cases do give a history of nipple discharge, but in most cases this does not occur. Periductal mastitis in minor form is no more apt to appear in breasts that have lactated than in those that have not, and multiple lactations do not play a part. We do not have enough data to state whether or not this is true of the most marked cases that present in a clinical form with segmental localization.

The presence of periductal mastitis in either cancerous or noncancerous breasts does not materially influence the occurrence of lesions other than those already mentioned as being fundamentally concerned in the process. When other lesions such as cysts and noncancerous proliferative processes are present, they never appear to begin as a result of periductal mastitis, stasis and distention of ducts or fat necrosis.

Any differences in cancerous and noncancerous breasts that show periductal mastitis are unimportant ones and depend almost exclusively on age distribution of cases. In none of the 300 cases of cancer could we trace the source of mammary carcinoma to periductal mastitis and its related lesions. The tracing of cancer to this source would, in our opinion, depend upon the demonstration of histologic transitions in the epithelium at such foci. Previously, it has been stated that the most common alteration in epithelial cells at such sites is metaplasia, usually of minor degree, and in some instances the production of true squamous characters. Another epithelial change fairly common at areas of periductal mastitis and stasis and distention is slight epithelial piling-up and loosening. This change is a minor one, usually seen in medium and larger ducts, and seems to be little more than trivial hyperplasia that desquamates rapidly. The stasis and distention as well as the periductal mastitis are usually slight in such areas, and it is almost invariable to find flattening and atrophy at sites of marked distention and periductal mastitis. It is not implied that an atrophic epithelium is unlikely to give rise to cancer. It can be said, however, that in the material studied here, no significant histologic atypism could be found in either atrophic or hyperplastic epithelium lining areas of stasis, distention and periductal mastitis. In the earliest mammary cancers seen by us in this and other material where the ducts were lined by typical cancer cells, periductal mastitis does not play the rôle of precursor.

VIII — THE MAMMARY LOBULES

The comparative examination of the character of the mammary lobules in cancerous *versus* noncancerous breasts has offered more difficulties than any other aspect of this morphologic analysis. That this has been the experience of other authors is indicated by the relative absence of detailed accounts of lobule abnormality. Perhaps these writers have felt the same major obstructing factor as we ourselves, namely, the problem posed by the question, what constitutes the normal lobule pattern of the human female breast and what changing aspects, if any, are imposed by the cyclic phases of menstruation? Insofar as we have been able to ascertain, there has been no morphologic survey of mammary lobules which has been based upon the examination of ideal material. Reports on breast tissue taken from autopsies have the disadvantage that they deal with specimens from chronic or acute diseases that may in themselves have been in part responsible for alterations in the lobule structure presented. Actually, the study of such breasts is a specific problem in itself, and should logically be prosecuted after a fundamental

normal has been established by study of "screened" material. The other source from which observations have been made is from surgical breasts, and these as a whole are *prima facie* abnormal organs. Even so, when one studies a large amount of such material and compares his findings with those of others, there seems no doubt that certain lobule patterns are more characteristic of one phase of the cycle than another. We have been able to study a limited amount of selected autopsy material and, in addition, over 300 surgical breasts from patients in whom menstrual dates were known. Our findings are in more or less agreement with the descriptions furnished by Rosenburg,[3] Dieckmann,[4] Polano,[5] and Geschickter,[6] and divergencies will not be elaborated here in histologic detail. Structural features that we consider indicative of various phases of the menstrual cycle are presented with explanatory notes in Figures 26 through 33.

After the study of material of the type mentioned above, much remains that is unsatisfactory. A vast majority of these breasts present a distinct variation in lobular structure, and it is the unusual gland that possesses even a moderately homogeneous picture. Certain of the lobule patterns when charted in relation to certain stages of the menstrual cycle will be found more commonly in the lutein phase, for example, and yet the chart will show these same types during the follicular phase and *vice versa*. Only a trend is shown. Added to this there are other types of lobules that show no relation at all to the periodicity of the ovarian cycle, and, moreover, they embrace a wide variety of structure quite different from that of those lobules which seem more characteristic of either the follicular or lutein phase. In our lack of understanding of the significance of these latter structural types, we pursued their study under the premise that they may represent abnormal lobule configurations. Almost at once, it became obvious that the lobules adjacent to such expanding lesions as fibro-adenoma and cyst or lobules at the edge of a cancer showed a series of changes not encountered when these lesions were absent. Chief among the changes seen were intralobular edema, irregular contour and size of lobules and their epithelial components, lack of uniform layering of acinar epithelium and intralobular round cell infiltrate. These changes apparently represented an early stage in what can be called secondary lobule alteration. The later stage of this process was accented by decrease or nearly complete loss of lobular epithelial components, replacement by dense round cell infiltrate and decrease or disappearance of lobular edema. Finally, lobular units were completely effaced and their former sites marked only by residual round cell foci with perhaps hyalinized acinar remnants. Of all these changes the marked intralobular edema seemed most common. Often these alterations involved lobules as much as 2 cm. distant from the edge of a large, expanding lesion; they extended, as might be expected, a shorter distance when the expanding lesion was roughly 1 cm. in diameter. In any breast containing many cysts and/or other lesions causing peripheral pressure, it can be easily seen that lobule homogeneity will in some measure be disrupted.

FIG. 26

FIG. 27

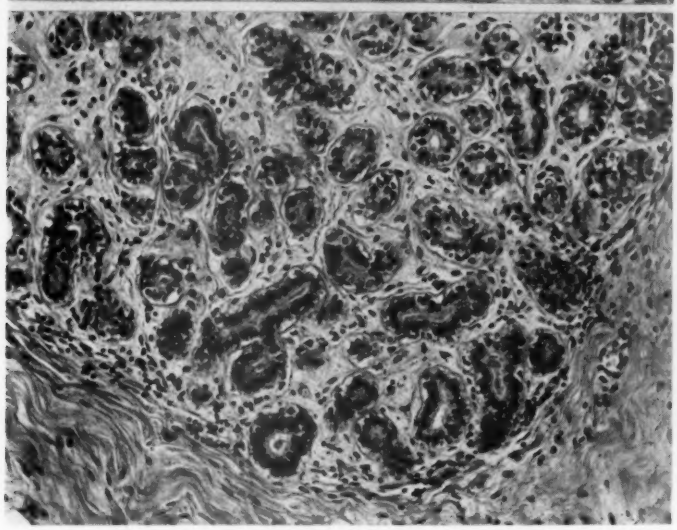


FIG. 26.—Section taken on first day of menstruation. Acini are numerous and closely spaced. Lumina are open and contain secretion. Lining cells cuboidal to columnar, cytoplasm rather abundant and pale. Cell arrangement orderly. Full size of lobule not shown in this cross-section. Stroma rather vascular and free from collagen. Occasional lymphocytes. Fully developed lutein phase of cycle. Appearance indistinguishable from many lobules seen in third month of pregnancy. Many lobules in this breast fail to show as marked luteinization.

FIG. 27.—Section taken on fourth day after onset of menstruation. Early involutional changes. Acini continue to be numerous. Some lumina remain open, some narrowed, many closed. Residual secretion can be seen. Fewer columnar cells. Orderly cell arrangement persists in some acini but with contracture of acini and obliteration of lumina, cells are piling-up in disorderly fashion. Stroma showing early condensation and increased numbers of lymphocytes as well as decreased vascularity.

FIG. 28

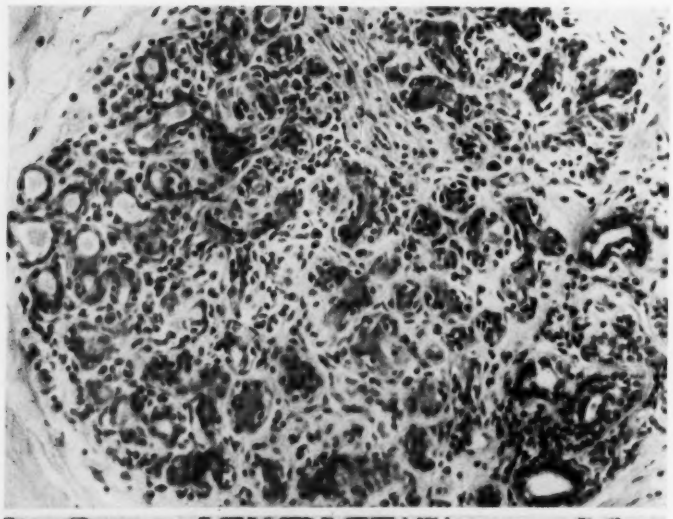


FIG. 29

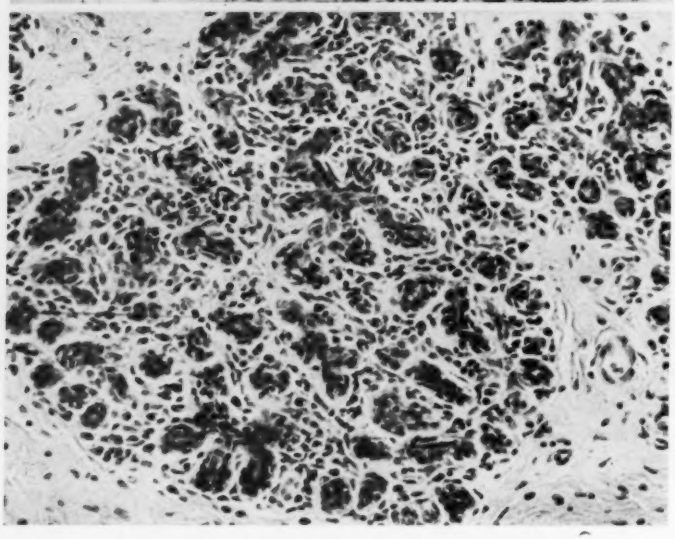


FIG. 28.—Section taken eight days after onset of menstruation. Further involutional changes. Process not entirely uniform but this is not unexpected. Central portion of lobule in advance of periphery. Some acini almost extinct. Increasing numbers of lymphocytes. (Compare with Figures 27 and 29)

FIG. 29.—From same section as Figure 28. Uniform and rather advanced involution. Acini still numerous but collapsed. Condensation of acinar cells. Reduction in size and nuclear pyknosis. Abundant lymphocytic infiltrate. Stroma somewhat less dense than ordinarily found eight days after onset of menses.

On further observation, secondary lobule alteration could be found in association with other breast lesions. Those lobules distal to an intraductal papilloma or comedocarcinoma were nearly always adversely affected. The general trend in these instances was toward atrophy following in the wake

FIG. 30

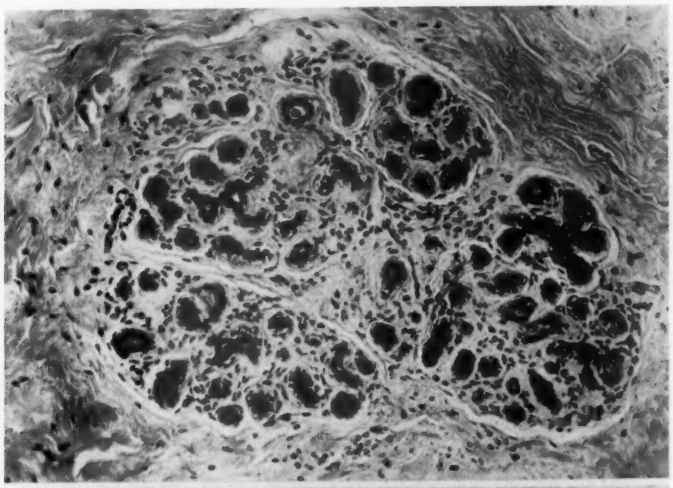


FIG. 31

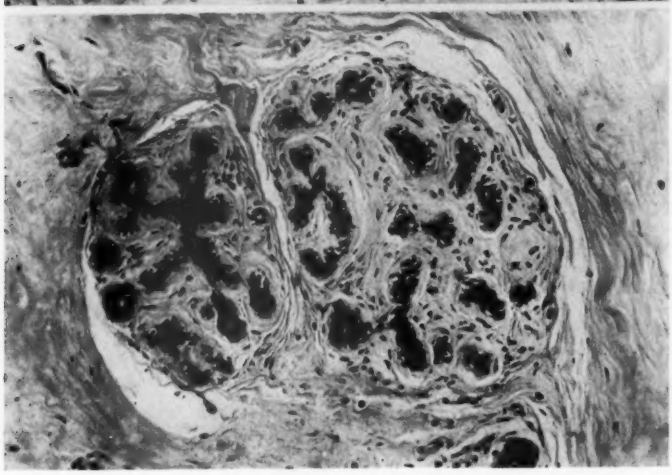


FIG. 30.—Section taken 12 days after onset of menstruation. Involution nearly complete. Acini less numerous, more widely spaced. Intervening stroma denser. Lymphocytes still present.

FIG. 31.—From same section as Figure 30. End-point of physiologic involution. Few acini remain and these in collapsed state with hyaline connective tissue condensation about some. Remainder of stroma dense and practically free from lymphocytes.

of, and dependent upon the degree of the induced duct dilatation, stasis of duct content and periductal mastitis. In another section we have discussed the secondary formation of duct stasis, distention and periductal mastitis due to pressure from cyst, fibro-adenoma and cancer. Thus, any expanding

lesion of the breast may not only cause lobule alteration locally through pressure alone, but also at a greater distance by interference with adjacent ducts, the effects of which interference are detected in their corresponding lobular terminations. As expected, when the lesion complex of duct stasis,

FIG. 32

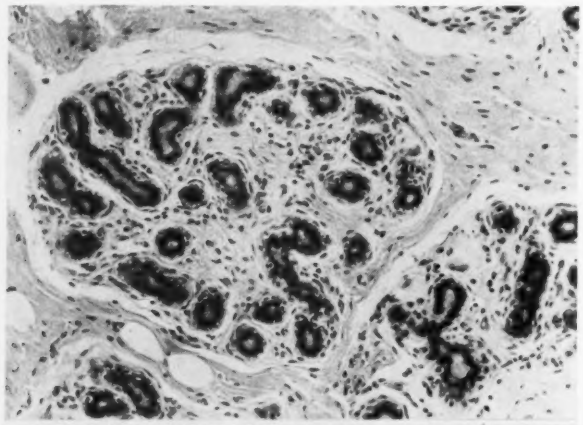


FIG. 33

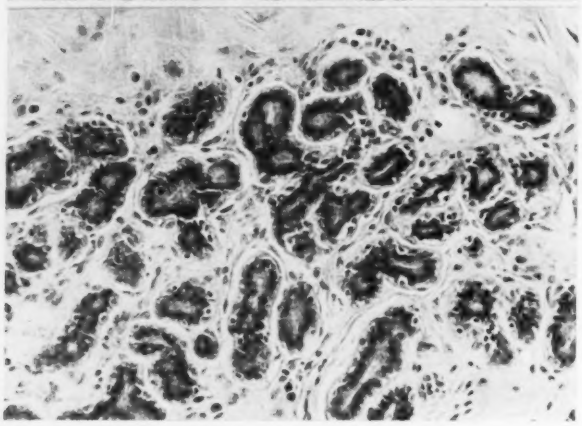


FIG. 32.—Section taken 15 days after onset of menstruation. Stage of reactivation. Note loosening of stroma as if in preparation for acinar hyperplasia. Connective tissue cells larger and less elongated. Occasional mitoses of these cells present but not visible at this magnification. Acinar lumina reestablished with lining cells assuming coherent arrangement. Nuclei remain dark.

FIG. 33.—Section taken 22 days after onset of menstruation. Characteristic corpus luteum effect. Multiplication of acini. Lumina present but not yet crowded with secretion. Lining cells larger and taller. Cytoplasm more abundant and nuclei relatively pale. Occasional mitoses can be seen with difficulty.

dilatation and periductal mastitis occurs in primary form, the lobules supplied by these ducts show the same changes as seen when the aforesaid lesion-complex of duct dilatation, stasis and periductal mastitis is of secondary type.

Those portions of breast tissue free from expanding lesions did not show the type of change referred to as secondary lobule alteration. In

sections of such tissue, however, it was common to see lobule patterns that did not fit the pictures associated with expected cyclic changes. The structural types seen were several in number, and as a general group may be referred to as primary lobule alteration. In some instances the lobules were uniform in appearance, and when such was the case, they tended to assume one of two forms. In the first of these the lobules were very few, they were quite small, the acini were scanty and reduced in size. The intralobular connective tissue was neither edematous nor dense, and periacinar hyaline was inconspicuous. Often there was considerable fat replacement of fibrous stroma. In short, this was a reproduction of an atrophic breast, and was what would be seen in the breast of a postmenopausal woman. On repeated occasions this sort of lobule pattern has been seen in women far short of the menopause. Extreme examples may be seen in the early twenties. Little or no difference was apparent regardless of the stage of the menstrual cycle during which the tissue was obtained. No accurate explanation can be made when such cases have normal menstrual histories, and such is usual in the cases seen thus far. The general impression is that such breast tissue may be refractory to hormonal influences. Verification of this hypothesis obviously depends upon demonstration of at least normal cyclic output of both the follicular and luteinizing hormones, since the mere existence of a normal menstrual cycle clinically perhaps tells us nothing of actual hormone patterns.

In the second type of primary lobule alteration where homogeneity of structure existed, the following was seen: The number of lobules was neither increased nor decreased. They were chiefly of average size. The intralobular connective tissue was abundant, loose and edematous. The epithelial components were very few in number but of large size, and the lining cells were often piled up in three to four layers and were rather apolar in arrangement. Seldom was periacinar hyaline a prominent feature. The most extreme examples of this type furnished at least a superficial resemblance to gynecomastia, particularly when the epithelial components of the lobule were very few in number. Again, this type of lobule structure has been encountered repeatedly without relation to any particular phase of the menstrual cycle. Any proposal that such a picture is the result of excess follicular hormone meets the embarrassment of one's inability to present the required proof by chemical assay.

The two types of primary lobule alteration just discussed are relatively infrequent, each being seen in about 5 per cent of surgical breasts. Far more common is a third form of primary lobule alteration in which the lobule pattern is unbalanced and irregular. A description of these changes is extremely difficult to put into words. The principal character is the heterogeneity which makes it utterly impossible to predict from sections at what stage of the menstrual cycle the tissue was obtained. Certain lobular groups suggest the lutein phase, while adjacent ones seem more characteristic of the follicular phase. Still others partake of neither of these phasic types. Sometimes the structure resembles the florid phase of lobular sclerosing adenosis, and in the

same section foci may occur that demonstrate the regressive phase of the same process. Still other lobules appear to be undergoing atrophy very much as in a senile breast, while others suggest an early phase of cyst formation as manifested by marked acinar dilatation. Intralobular epithelial hyperplasia of "nonphysiologic" kind is seen. This is commented on at a further point in this section. Added to these are "metaplastic" changes in which the acinar epithelium becomes flattened and almost epidermoid in character; or perhaps the acinar epithelium is seen in various easily traced stages of transformation to the so-called apocrine type. It is reasonable to assume that when such complex lobule arrangements are met, they represent multiple epochs of abnormal proliferation and involution, some of which may have occurred long before the specimen was secured.

To refer such changes as these to hormone imbalance is still problematical, and practically all of the evidence on human breasts comes from somewhat indirect sources. These sources include (1) the résumé of material which indicates certain types of lobules to be more characteristic of the follicular or lutein phase of the cycle; (2) the study of the human female breast under known preponderance of the corpus luteum hormone, that is, in pregnancy; and (3) the study of the male breast under conditions of known excess of female hormone, that is, in gynecomastia. Interesting observations could be made if one could secure breast tissue from patients who, on curettage, are shown to have glandular and cystic endometrial hyperplasia. The number of cases required to enable proper evaluation is discouraging. When one applies the structural evidence from sources that are available and makes comparisons with surgical breast preparations, it is difficult to deny a probable relationship to hormone imbalance. It seems possible that the implied imbalance need not require an excess of one or the other ovarian hormone; perhaps a subnormal amount of one or the other is sufficient. There is evidence that certain lobules are either more or less liable to hormone stimulation than are others. This is partially demonstrated by sections of the breast in various stages of pregnancy. Not every breast in the fifth to sixth week after the last menstruation shows the same degree of response, and as a matter of fact in some cases, one could not be sure of the existence of pregnancy from the sections, the appearance being so similar to that seen in a normal premenstrual breast. Even in the third trimester of pregnancy very small numbers of lobules may either appear almost totally unresponsive or much less well-developed than the vast majority of the lobular units. The rate of involution of individual lobules following pregnancy is also subject to demonstrable variation. Moreover, in examining a large number of breasts taken from one to ten years after the menopause, it is remarkable to note how capricious may be the rate of lobular atrophy.

The implications brought forward in the foregoing received some support when, late during the progress of this general study, we had the opportunity to examine breast material from another source. Through the aid of Doctor Sophie Spitz, and the courtesy of the Medical Examiner's Office of New

York City, specimens of both breasts and the endometrium were obtained. These were from cases of sudden death due to accident, homicide, or natural diseases, the latter being noninfectious in nature. There were two interrelated purposes in securing this material from cases of sudden death. First of these was to gain a more accurate insight into the frequency of the lesions of so-called chronic cystic mastitis in the breasts of the female population at large. The second was to ascertain the "average" appearance of the mammary lobules during the various phases of the menstrual cycle, as indicated by comparison with simultaneously taken sections of endometrium in cases without debilitating chronic disease. There were 27 such cases aggregating 54 breasts. Two of the cases were in the decade 10–20, three in the decade 20–30, thirteen in the decade 30–40, and nine in the decade 40–50. Not less than eight and an average of ten blocks were cut in each case, considerably more abundant sectioning than was done in the series of 500 cases reported here in detail. A thorough summary of this additional material will not be made here, but will be reported at a later date. The total number of cases is admittedly small, but there was so much structural contrast with the group of surgical breasts that some general comment seems warranted.

The lesions that have been presented in previous sections as constituting the complex of so-called chronic cystic mastitis were not absent in the material from cases of sudden death, but they were far less plentiful and by no means of as marked degree as seen in the cancerous or noncancerous surgical breasts. This was preeminently true in regard to gross lesions and equally true as regards microscopic lesions. The more plentiful sectioning of the material from instances of sudden death is, in our opinion, reinforcing, in that it affords less chance of failure to detect abnormalities.

The lobule status in the postmortem material was vastly different from that in the surgical material. In surgical breast material from premenopausal women, we find only about 10 per cent of cases that have enough homogeneity of lobule structure to justify a prediction of the phase of the menstrual cycle. After a certain degree of lobule imbalance is attained, any estimate is pure guesswork. Two of the 27 cases of sudden death showed advanced postmortem changes and were unsuitable for lobule or endometrial determinations. Three of these cases had atrophic endometria and were regarded as postmenopausal. Of the 22 remaining cases, two showed primary lobule alteration which made estimate of the stage of ovarian cycle unfeasible. Three of the cases showed the atrophic type of breast unsuitable for determining cyclic phases. There were 17 cases with uniform lobule structure which enabled one to estimate the phase of the menstrual cycle. In 16 of these 17 cases, the independent predictions of the cyclic phase by two observers proved correct, as controlled by the accompanying endometrial pattern. The prediction reported as a failure was correctly made by one observer. The sections of endometrium were, of course, not consulted until after the examination of the breast tissue. Excluding breasts and endometria showing too advanced postmorten change and those that were postmenopausal, there

were 22 cases. In 16 of these (72 per cent) it was possible to predict from the breast sections the phase of the menstrual cycle. This is in high contrast to the figure of 10 per cent obtainable by us in surgical breasts. In short, the homogeneity of the lobular structure of these breasts from cases of sudden death was directly contrary to the disordered lobular structure found in the surgical breasts. The far lesser incidence of the lesions of "chronic cystic mastitis" and the comparative absence of lobule alteration in the control (sudden death) breasts, combined with the high frequency of these lesions in the surgical breasts, suggests a close relationship between lobular alteration and the lesions we have presented in another section as constituting the complex of so-called chronic cystic mastitis. Perhaps certain forms of lobule alteration are an integral part of that complex.

In studying the occurrence of lobule alteration in the group of 300 cancerous and the 200 noncancerous breasts, observations were limited to the decades 30–40 and 40–50. Secondary lobule alteration was so common that no figures are given, and, moreover, it has already been stated that, anatomically, such changes seem secondary to pressure or duct stasis and associated lesions. The figures given in Table XIX concern only primary lobule alteration, as it has been described in the foregoing.

Table XIX indicates little except that in surgical material these lobule alterations are common, and that they are considerably more frequent in the later decade, as has been shown in preceding tabulations to be true of other lesions concerned in so-called chronic cystic mastitis.

TABLE XIX

INCIDENCE OF PRIMARY LOBULE ALTERATION

Decade	In Noncancerous Breasts Frequency in Per Cent	In Cancerous Breasts Frequency in Per Cent
30–40	36	34
40–50	52	48

The previous comments on lobule structure have referred to two general types of lobule alteration, primary and secondary, and were intended to direct attention to what may be considered abnormal lobule structure. It seems necessary here to discuss in some detail the problem of epithelial hyperplasia in lobules. Epithelial hyperplasia can be seen in lobules that show either primary or secondary alteration. A good deal of effort has been put forward in trying to establish what constitutes pathologic hyperplasia of lobular epithelium. The necessary criteria arrived at after prolonged consideration demand that the lobule under examination have an appearance dissimilar to that seen as a phasic pattern of the menstrual cycle or of pregnancy; the number of layers of lining epithelium must be greater than two (unless there is obviously a focal pile-up). If any part of a lobule shows such changes, epithelial hyperplasia is considered present. If such changes are limited to a single acinus, it is extremely uncommon in our experience. On many occasions, however, a relatively small part of a lobule may be affected. The occurrence of this sort of epithelial hyperplasia was

tabulated for the same material in which the incidence of lobule alteration was determined (Table XX).

TABLE XX

INCIDENCE OF INTRALOBULAR EPITHELIAL HYPERPLASIA

Decade	Noncancerous Breasts Frequency in Per Cent	Cancerous Breasts Frequency in Per Cent
30–40	14	16
40–50	22	34

FIG. 34

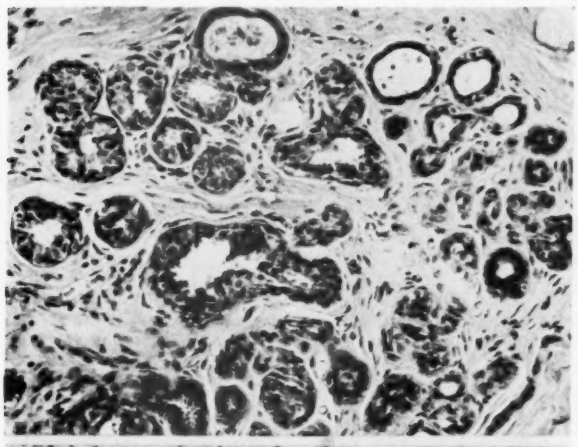
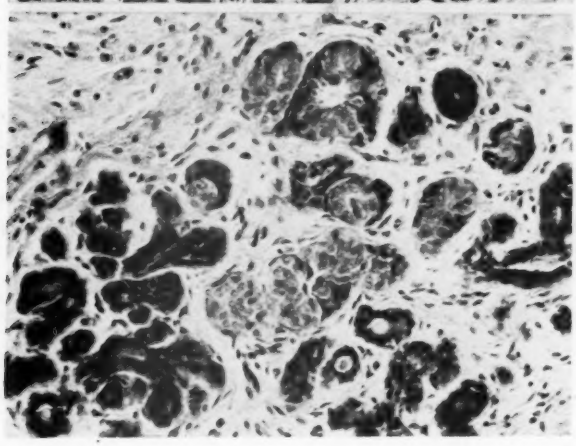


FIG. 35



FIGS. 34 and 35.—Lobule patterns dissimilar to any seen as phasic variants of the ovarian cycle. Structural imbalance with multilayered lining cells in disorderly arrangement.

The degree of epithelial hyperplasia in lobules, as one would anticipate, varied between broad limits from simple multiplication of lining layers to complete plugging of acinar lumina. A considerable experience is necessary before one's designations of epithelial hyperplasia in lobules are accurate and repeatable. Our plan was for each observer to make independent

recordings, compare results, review material where discrepancies occurred, and continue until each individual's observations were reproducable by the other. Several hundred breasts were studied in this manner before the above tabulations were made.

In a former paper[7] the existence of and the histologic features of lobular

FIG. 36

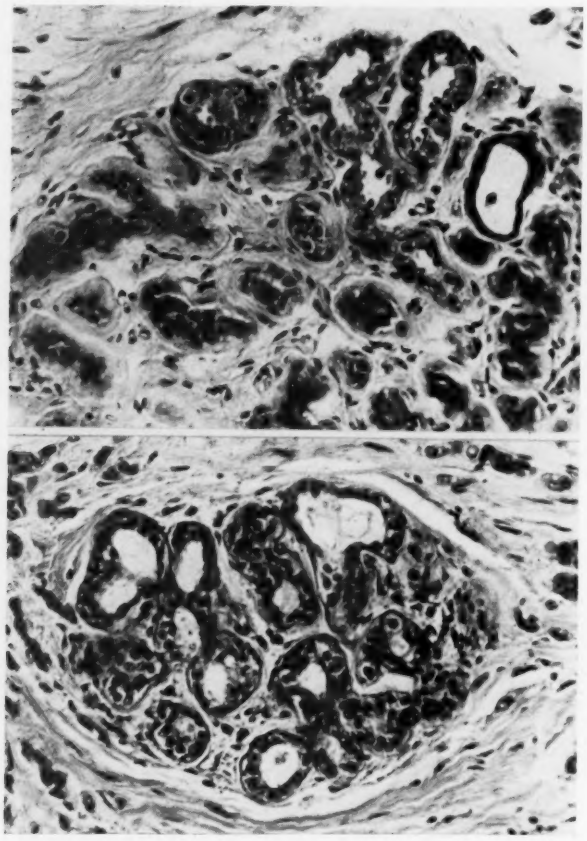


FIG. 37

FIG. 36.—Lobular alteration, with pathologic hyperplasia of epithelium.

FIG. 37.—Appearance superficially suggesting corpus luteum phase of menstrual cycle, but there is stratification of lining cells, lack of coherent grouping and difference in cell size and staining properties. Moreover, patient beyond the menopause.

mammary carcinoma *in situ* were discussed. In addition, a brief description of the infiltrating phase of this type of mammary carcinoma was given. At that time no effort was made to depict histologic levels of lobular epithelial change that fell short of the fully developed *in situ* lesion. It was felt that such changes must exist, but we were not sure of their identity. The large mass of material examined in the past few years has made us much more confident of the earlier transitions to lobular mammary carcinoma *in situ*.

FIG. 40

FIG. 38

FIG. 38

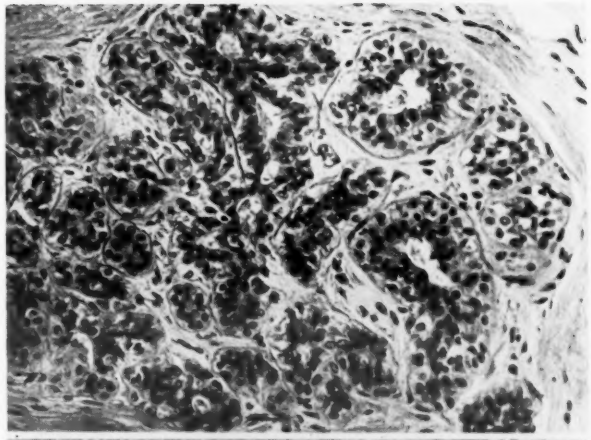


FIG. 39

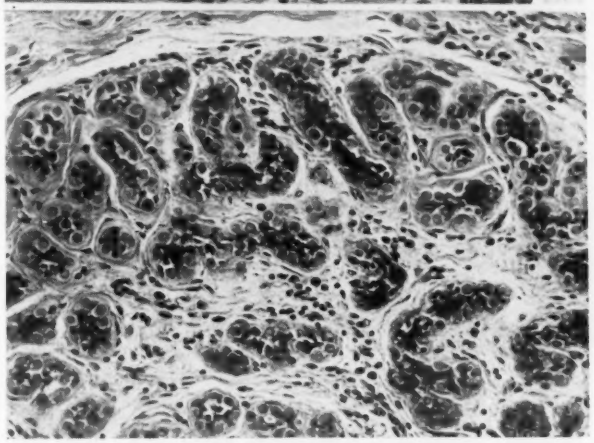


FIG. 38.—More advanced stage in hyperplasia of lobular epithelium. Structure distinctly atypical with deep stratification or plugging of lumina. Lack of polarity with pleomorphism and variable staining qualities. Mitoses seen, but not at this magnification. (Compare with Figures 37 and 39)

FIG. 39.—Interpreted as an early stage of lobular carcinoma *in situ*.

FIG. 40

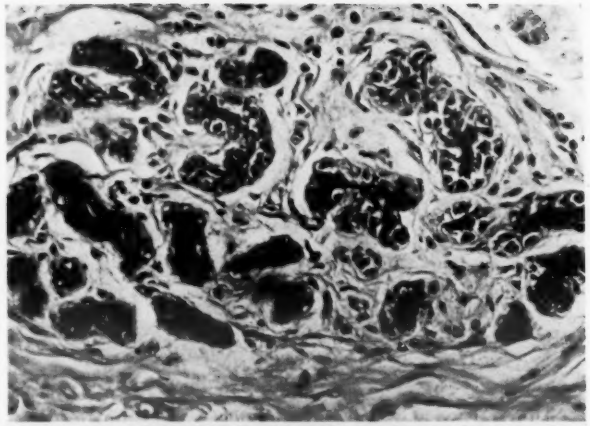


FIG. 41

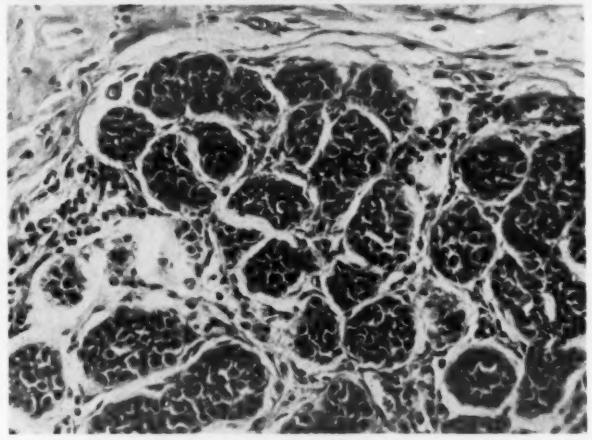


FIG. 40.—Another early phase of lobular carcinoma *in situ*. Note partial involvement.

FIG. 41.—Fully developed lobular carcinoma *in situ*. Acinar outlines still distinctly maintained.

To write a word-formula for the identification of these subtle alterations is beyond our powers. The photomicrographs shown in Figures 34 through 43 illustrate variable degrees of lobule alteration with progression to lobular mammary carcinoma both *in situ* and in an early infiltrative phase. These may suffice in part, but they cannot substitute for actual retinal images. Once the actual histologic pictures are grasped, they appear to one as highly

FIG. 42

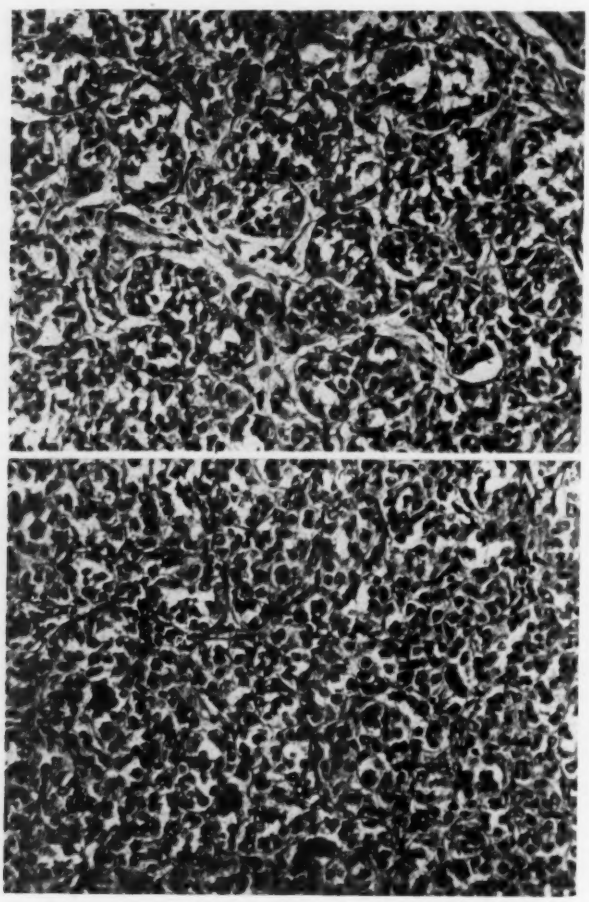


FIG. 43

FIG. 42.—Further progression of lobular carcinoma *in situ*. Integrity of individual acini difficult to detect at all points.
FIG. 43.—Merging of acini and start of infiltrative stage.

characteristic and separable from other more common pictures of hyperplasia in lobules.

We regard certain atypical hyperplasias as transitional stages in the development of *in situ* lobule cancer. In a preceding section, it has been shown that one of the chief differences between cancerous and noncancerous breasts was the far greater likelihood that the cancerous breasts would show

duct papillomatosis of atypical structure. For this reason it seemed necessary to investigate atypical hyperplasia in lobules for the same relationship. In the material used for other lobule studies, there were 100 noncancerous breasts equally divided between the decades between 30 and 50 years. Not a single case was found in which there was atypical hyperplasia in lobules. This absolute absence is one of chance, since in about 500 noncancerous breasts seen yearly at Memorial Hospital, this atypical form of hyperplasia is seen about half a dozen times. We do not refer here to true lobular carcinoma *in situ* but the less advanced lobular alteration.

In 32 cancer cases between the ages of 30–40 and 50 cancer cases between the ages 40–50 there were six which showed the atypical form of intralobular epithelial hyperplasia. In four of these six cases, the cancers had the infiltration pattern so characteristic of cancers of lobule origin. In this group of 82 cancers, some form of epithelial hyperplasia in lobules was seen in 22 cases. In those 22 cases there were nine lobular mammary carcinomas, an incidence of 40 per cent, while the over-all incidence of lobular carcinoma is only about 5 per cent. These findings lead us to believe that the epithelial hyperplasias discussed do have a positive relationship in the development of mammary carcinoma of lobule origin.

In comparing the lobular structure of cancerous and noncancerous breasts, abnormal types are common in each group. One fundamental difference is found. This is the much more pronounced tendency for the lobules of breasts with cancer to show intralobular epithelial hyperplasia of atypical sort.

(To be continued)

CURLING'S ULCER IN EXPERIMENTAL BURNS*

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ULCERATION OF THE DUODENUM associated with burns has occurred in 12 per cent of animals utilized in an experimental study of burns projected by the National Research Council, and carried out at the Henry Ford Hospital. The material on which this presentation is based consists of 34 instances where ulceration of the duodenum was found associated with the experimental burn. An analysis of this material seems worth while in view of the fact that: (1) Harkins[1] found only 98 Curling's ulcers in 680 burn cases reported up to 1938, of which 26, or 3.8 per cent, were confirmed by autopsy; (2) Curling's ulcers, that is ulcers of the duodenum subject to perforation and hemorrhage, have not been consistently produced experimentally; (3) this series shows a strikingly higher incidence in animals treated with bland dressings, such as sterile vaseline, in contrast to those treated with tannic acid, ferric chloride, silver nitrate and other tanning agents; (4) lethal complications of these ulcers have occurred in nine instances, hemorrhage four times, and perforation with peritonitis five times; and (5) the pathogenesis and the definite relation to burns have not been established.

Pack,[2] in 1926, and Harkins,[1] in 1938, made comprehensive reviews of duodenal ulcers associated with burns, first collected and described in detail by Curling[3] in 1842. Cooper,[4] in 1839, and Long,[5] in 1840, had reported individual cases previous to Curling's consideration of the subject.

Although the 3.8 per cent incidence of autopsied cases quoted from Harkins represents a large series, it should be kept in mind that the percentage varies in this group from zero to 36.5, and that in the larger series the incidence is relatively low—Erichsen,[6] 1895, 94 cases, or 2.1 per cent; Stewart,[7] 1923, 115 cases, or 1.7 per cent; Harris,[8] 1929, 138 cases, or 0.7 per cent; and Riehl,[9] 1930, 152 cases, or 3.3 per cent.

As to pathogenesis, Pack lists ten theories and Harkins 26. Only those hypotheses supported by some objective evidence, clinical or experimental, will be enumerated here.

1. Hyperacidity of gastric secretion.—Necheles and Olson,[10] 1941, found a great increase in gastric motility, and in a number of animals a considerable increase in the volume and acidity of the gastric secretion. Wilson,[11] 1935, failed to show hyperacidity in patients.

2. Action of burn toxin.—Harris,[8] 1929, ascribes Curling's ulcer seen in a three and one-half-year-old child to "protein metabolites" formed by digestion in the burned area. He believes this toxin produces focal necrosis and hemor-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Henry Ford Hospital.

rhage in the duodenal mucosa and that these are, in turn, transformed into ulcers by the pancreatic juice. Kapsinow,[12] 1934, pointed out from his work on rabbits that blood concentration results in stasis with rupture of the capillaries underlying the duodenal mucosa with tissue anoxia, necrosis and ulceration.

3. Blalock,[13] 1931, demonstrated low blood volume in burned animals, and Brooks and Blalock,[14] 1934, showed necrosis, congestion and hemorrhage in both the duodenum and adrenals after producing a low blood volume by slow bleeding. More recently, Freeman, *et al.*,[15] 1942, and Wiggers,[16] have shown congestion of the duodenum in hematogenic shock.

4. Perry and Shaw,[17] 1894, pointed out that in septic conditions petechiae occur in serous and mucous membranes throughout the alimentary tract, and expressed the opinion that these petechiae served as the initial lesion from which duodenal ulcers in both septic processes and in burns develop. Hertz and Digby,[18] 1913, and Stewart,[7] 1923, supported the view of Perry and Shaw, pointing out that the incidence of Curling's ulcers was reduced by antiseptic and aseptic surgical treatment.

EXPERIMENTAL PROCEDURES

The material forming the basis for this presentation consists of 32 instances of gastric and duodenal ulceration occurring in the course of 80 experiments in which third degree burns were produced over 50 to 60 per cent of the body surface, while the animals were under morphine and ether, or morphine and chloroform anesthesia. Following the procedure, liberal use of morphine and complete dressings kept the animals comfortable, as evidenced by the fact that they were active and retained a good food intake until the terminal stages.

In the first group of seven experiments involving large burns, two were dressed with sterile vaseline, four with tannic acid and one with sulfadiazine and lanolin. One vaselined animal survived only four days but the second lived eight days, and showed multiple small, punched-out duodenal ulcers. The other members of the group lasted from eight to 13 days, but failed to show ulceration.

Following this observation, a series of four animals, Nos. 3095, 3096, 3097 and 3098, were burned and dressed with sterile vaseline. Survival time was 10, 10, 13 and 10 days respectively. Numbers 3095 and 3097 had large, punched-out duodenal ulcers, measuring 2 x 1 cm. and extending down to the serosa. Number 3096 had multiple small ulcers, 1 to 2 Mm. in diameter in the prepyloric region of the stomach, while No. 3098 had a superficial mucosal ulcer, 1 x 1 cm., in the duodenum. All of this series showed extensive infection of the wound, *B. coli, B. proteus, B. lactis aerogenes, Streptococcus hemolyticus* and *nonhemolyticus, Staphylococcus albus* and *Cl. bifermentans* being isolated. Number 3098 showed *Streptococcus hemolyticus* in blood cultures. Terminally, the blood plasma proteins were 5.4 Gm., N. P. N. 75 mg., CO_2 17.7 vol. per cent, calcium 10.1 mg., and icterus index 15.

Out of the first seven animals burned and dressed with sterile vaseline the five living eight days or more showed infection of the wound and gastric or duodenal ulceration.

In the second group of experiments sterile vaseline, scarlet r. ointment and lanolin were used ten times, resulting in ulceration of the duodenum three times and of the stomach once.

FIG. 1

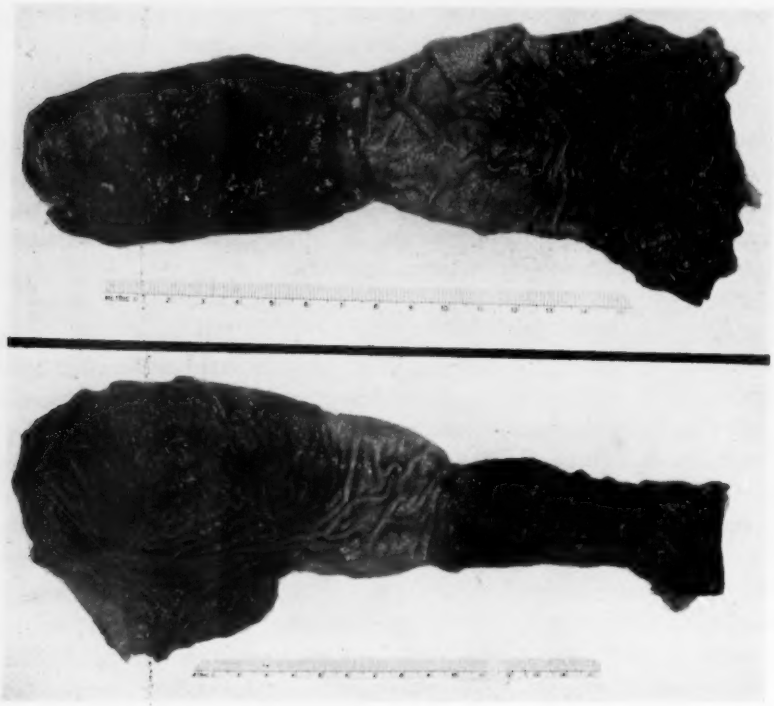

FIG. 2

FIG. 1.—Experiment No. 3180.—Burned 60 per cent of body surface with steam, under chloroform anesthesia. Dry dressing with 7.5 per cent tannic acid. Survival time four days. *Autopsy:* Liver large, congested; kidneys large, congested; duodenum and fundus of stomach showed marked edema and congestion.

FIG. 2.—Experiment No. 3157.—Received 150 cc. neutral tannic acid subcutaneously, while under ether and morphine anesthesia. Deeply jaundiced by third day. I.I. 50; blood sugar 76; hematocrit 67; survival time three days. *Autopsy:* Hemorrhagic pneumonia, bilateral; marked congestion of fundus of stomach and duodenum.

Combining the two groups outlined above, there are a total of 17 burns dressed with vaseline and similar dressings, with 11 resulting ulcerations, or an ulcer incidence of 64.7 per cent. It may be significant that two of this group failing to show ulceration were dressed with scarlet r. ointment and sulfadiazine-lanolin, respectively. Both of these had minimal infection as compared with the rest of the group.

In the second series there were 33 experiments. This differed from the first group in that all the dressings were of sterile vaseline. These dressings were not changed, and every effort was made to increase the survival time by special feeding and intravenous fluids. The average survival time was

only slightly prolonged, however, and five animals were lost during the first five days. Of these only one, No. 3220, showed duodenal ulceration. Ulceration was found 21 times, or in 63.6 per cent. Two animals, Nos. 3255 and 3259, had perforating ulcers, with peritonitis, and one died from hemorrhage (No. 3220). In one group of three, surviving 9, 10 and 10 days, respectively, the incidence of ulcer was 100 per cent, and in nine successive experiments only one failed to show ulceration. This failure was possibly due to the fact that we succeeded in keeping the animal alive but five days.

In reviewing the second series of experiments, the loss of appetite, loss of weight, necrosis and infection of the wound, the marked loss of plasma into the dressings, the high nonprotein nitrogen of the blood, low CO_2

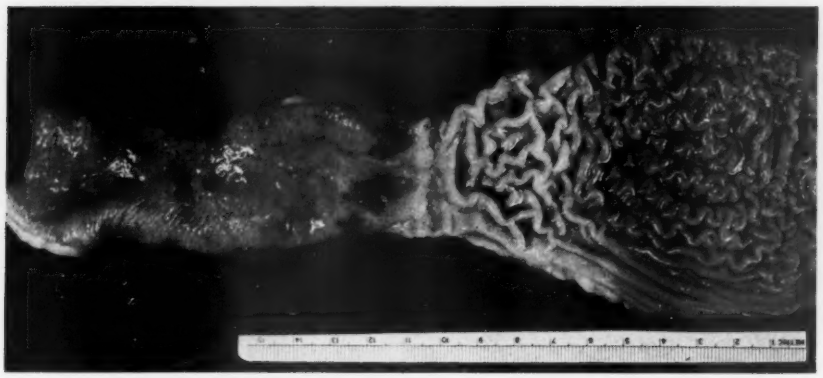

FIG. 3.—Experiment No. 3130.—Burned 60 per cent body surface, under chloroform and morphine. Dressed with sterile vaseline and gauze. Survival time six days. *Autopsy:* Two large mucosal ulcers of duodenum, associated with swelling and edema of the duodenal wall.

combining power of the blood, and the frequent coma with convulsions are clinical observations to be noted. At autopsy, the high incidence of acute ulceration of the duodenum, with no other equally consistent pathologic finding except the congestion and parenchymatous degeneration of the liver and kidneys is striking.

DISCUSSION.—In the first series there were 47 third degree burns involving from 50 to 60 per cent of the body surface, with 13 showing ulceration of the duodenum or stomach. Thirty of these burns were dressed with tanning agents, such as tannic acid, ferric chloride, and silver nitrate. In this group ulceration occurred only twice, or in 6.6 per cent, and then only in those having wet dressings. Of the 17 dressed with vaseline, lanolin and scarlet r. ointment 11, or 64.7 per cent, showed ulceration. In the second series of 33 animals with burns of similar type all were dressed with sterile vaseline and 21, or 63.6 per cent, showed duodenal ulceration.

The gross examination of the duodenal ulcers reveals erosions from the most superficial mucosal lesions to penetrating incisive lesions with hemorrhage or perforating punched-out lesions, with peritonitis. The inflammatory infiltration is mild or absent in most cases, with acute exudate reaction found in only one section. A few healed ulcer craters and large scarred areas of the duodenal wall were observed.

Although duodenal ulcers were encountered in animals living from six to 23 days, the marked edema and congestion of the duodenum, and less frequently of the stomach, in one to three days after the burn, has to be given consideration as a basic or underlying lesion, especially since it has

FIG. 4

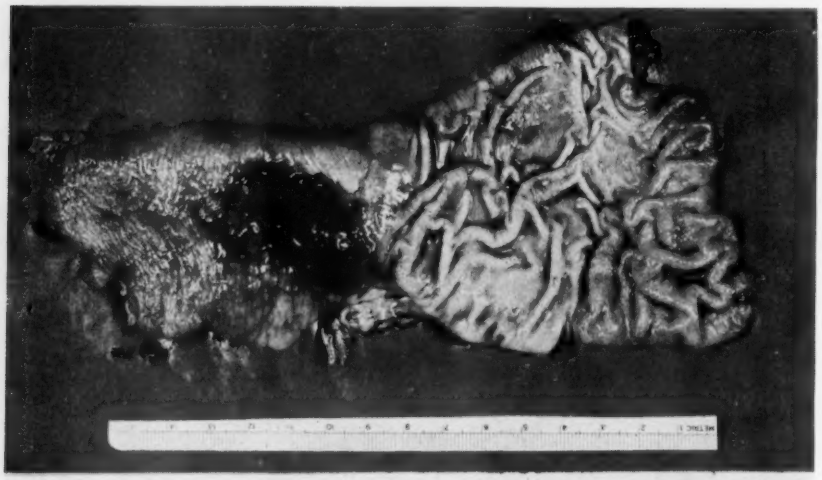

FIG. 5

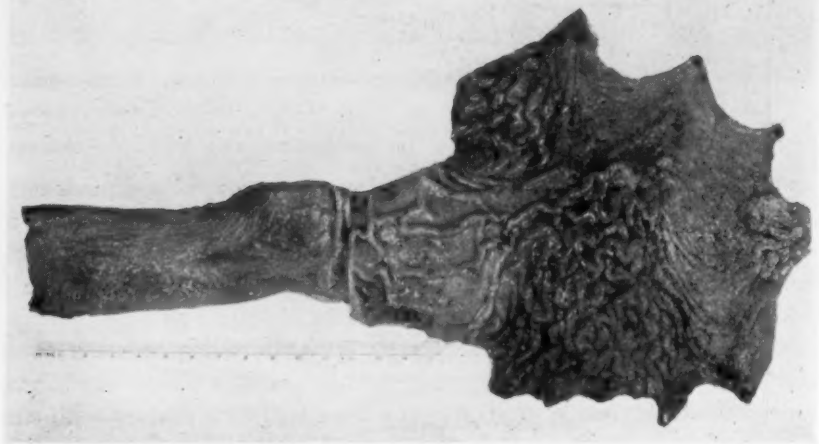

FIG. 4.—Experiment No. 3142.—Burned 60 per cent body surface, under morphine and chloroform anesthesia. Wet dressing with 7.5 per cent tannic acid jelly. Remained in good condition for eight days, then began to pass blood per rectum. Died on ninth day. *Autopsy:* Wound not tanned but shows extensive necrosis and severe infection. Intestine filled with fresh blood coming from two ulcer craters in duodenum. One crater has large clot adherent.

FIG. 5.—Experiment No. 3258.—Burned 60 per cent body surface. Dressed with sterile vaseline and gauze. Showed extensive necrosis and infection. Survival nine days. *Autopsy:* Marked congestion of stomach and duodenum with multiple small ulcers.

been demonstrated in other types of experimental shock. Indeed, this lesion seems another manifestation of the pathology of shock comparable to the early engorgement and congestion in the liver, which probably initiates the degenerative or necrotic changes in that organ.

A comparison of the gastric contents, both fasting and after 150 cc. of 5 per cent alcohol, of the normal and that of the burn dog at various stages shows that both the free hydrochloric acid and the total acid are reduced sharply rather than increased. This is in agreement with Wilson's[11] findings in the human, and not in accord with Necheles and Olson.[10] The other significant finding in the gastric contents was the blood, frequently seen as shreds and clots, and giving strongly positive chemical tests. This, coupled with the appearance found at autopsy, emphasizes the damage to the mucosa, preceding ulceration or in the absence of the same (Table I).

FIG. 6

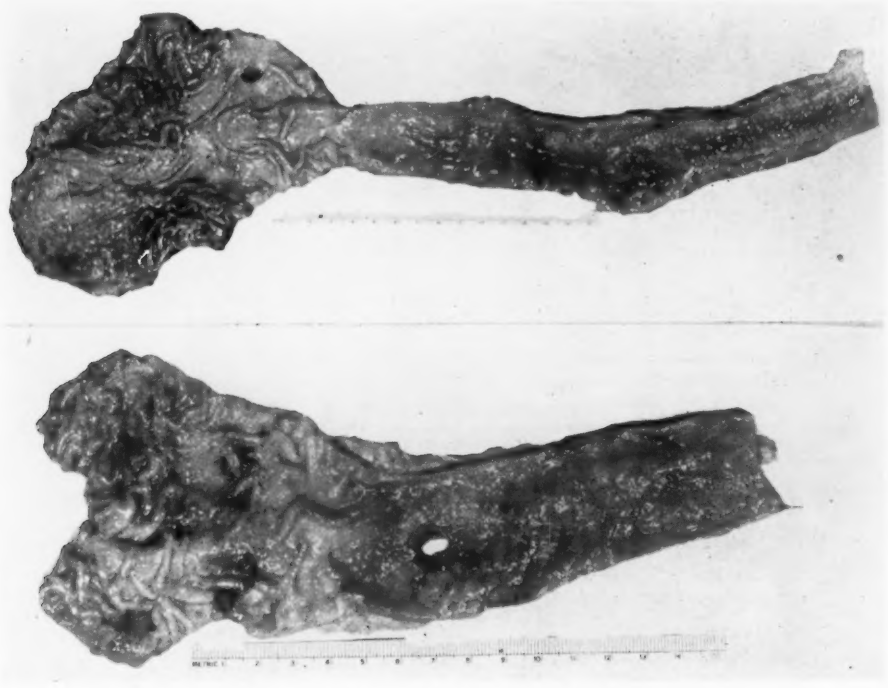

FIG. 7

FIG. 6.—Experiment No. 3262. Burned 60 per cent body surface. Vaseline and gauze dressing. Animal ate well for first ten days. Gastric analysis on eleventh day: Free HCl 6, total acids 58, occult blood +++. Showed extensive necrosis and infection. Survival 12 days. *Autopsy:* Stomach showed single ulcer, 1 cm. in diameter, pyloric region; duodenum—multiple smaller ulcers.

FIG. 7.—Experiment No. 3255.—Burned 60 per cent body surface. Dressed with sterile vaseline and gauze. Showed extensive necrosis and infection but ate well for first eight days. Survival time ten days. *Autopsy:* Abdomen distended with generalized peritonitis. On opening the duodenum there is a perforating ulcer, 1 cm. in diameter, with small erosions nearby.

Hyperacidity as explanation of Curling's ulcers has no support from our data, but normal acidity may be sufficient to cause ulceration in the edematous, congested mucosa of these burn animals. Further, it is quite possible that the usual alkalinity of the duodenal contents is reduced by mucosal damage and the developing general acidosis.

The liver showed extensive parenchymatous degeneration, especially at

the center of the lobule, but not the characteristic central necrosis except in those cases treated with tanning agents.

The kidneys were large and congested, with infarcts and cortical abscesses in about 5 per cent. Acute parenchymatous degeneration was regularly found.

The lungs usually showed edema and congestion with frequent lobular consolidation in the dependent portions.

TABLE I

GASTRIC ANALYSES

Dog No.	Specimen	Free HCl	HCl Def.	Total Acids	Guaiac
Normal dog	Fasting	24	0	90	Neg.
	15 mins.	10	0	25	Neg.
	30 mins.	2	0	20	Neg.
	45 mins.	2	0	18	Neg.
	60 mins.	0	10	24	Neg.
Normal dog	15 mins.	0	6	10	Neg.
	30 mins.	0	4	8	Neg.
	45 mins.	2	0	12	Neg.
	60 mins.	8	0	20	Neg.
3263 (6th day)	Fasting	2	0	12	++++
	15 mins.	4	0	6	Neg.
	30 mins.	4	0	8	Neg.
	45 mins.	14	0	22	++
	60 mins.	22	0	30	++++
	75 mins.	8	0	22	++++
3265 (6th day)	Fasting	10	0	12	++++
	15 mins.	2	0	10	Neg.
	30 mins.	0	4	2	Neg.
	45 mins.	0	2	12	++++
3265 (8th day)	Fasting	2	0	8	++++
	15 mins.	2	0	10	++++
	30 mins.	0	4	12	++++
	45 mins.	0	2	4	++++
	60 mins.	0	4	14	++++

Careful gross and microscopic examination of the brain was made in those animals particularly which showed coma and convulsions. Grossly, there was marked engorgement of the cerebral vessels but actual hemorrhage and encephalomalacia could not be made out. Microscopically, the hypothalamus was given special attention because of the relation of lesions of this area to ulceration of the intestinal tract, as pointed out by Cushing. Pericellular and perivascular edema was striking, with cuff hemorrhages about the vessels in a few instances. Small areas of devastation necrosis in the hypothalamus were present in one animal.

The 63 per cent incidence of Curling's ulcers in the two series of animals burned and dressed with vaseline and other bland applications, as contrasted with the 6 per cent incidence in the group burned in a similar manner and dressed with tannic acid or other tanning agents, indicates that an analysis of the two groups may suggest etiologic factors. The animal whose wound is dry-tanned loses very little plasma from the body, although the area

FIG. 8

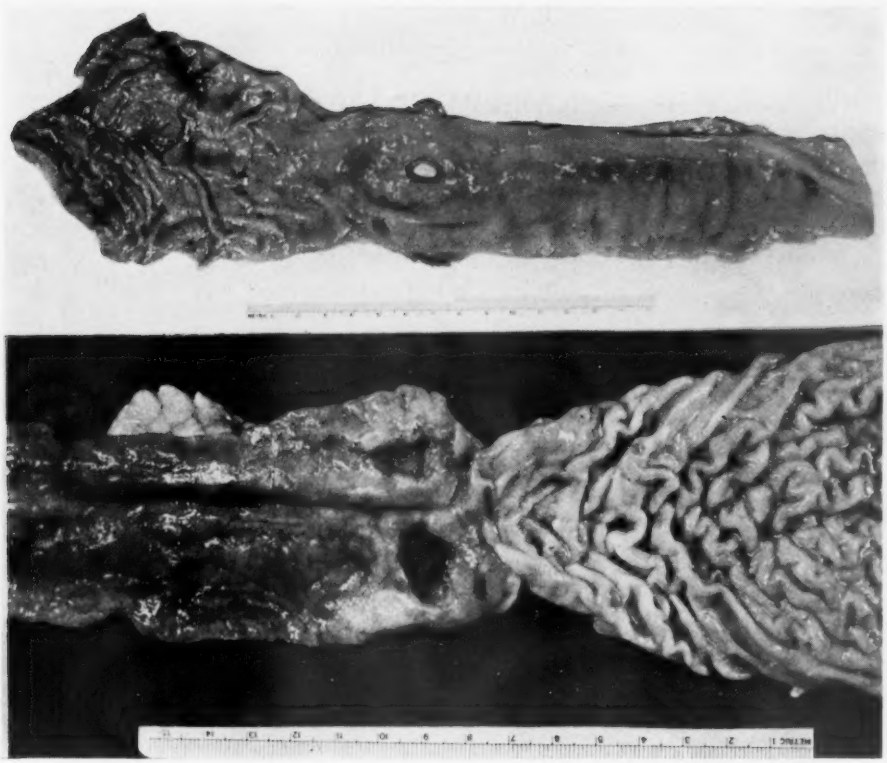

FIG. 9

FIG. 8.—Experiment No. 3259.—Burned 60 per cent body surface. Dressed with sterile vaseline and gauze. Extensive necrosis and infection of wound but appetite well maintained for first nine days. Survival time 11 days. *Autopsy:* Much free fluid in abdominal cavity and a perforating ulcer in the duodenum, 1.5 cm. in diameter. There are several smaller erosions in both the stomach and the duodenum.

FIG. 9.—Experiment No. 3097.—Burned 60 per cent body surface, under morphine and chloroform anesthesia. Dressed with sterile vaseline and gauze. Remains comfortable, eating and drinking fairly well. Cultures from wound on fifth day show both *hemolytic* and *nonhemolytic Streptococci, Staph. albus,* and eight other nonpathogenic bacteria. On the sixth day plasma proteins 515 mg. per cent; hematocrit 45. Survival time nine days. *Autopsy:* Two large perforating duodenal ulcers.

FIG. 10.—Dog No. 3249.—Photomicrograph showing small punched-out ulcer extending through mucosa and submucosa. No evidence of inflammatory reaction. (Low power)

beneath is always very edematous. The infection in such a wound is usually slight or absent up until the fourth or fifth day, when marginal separation of the eschar begins. The animal is comfortable and eats well after the first 36–48 hours. Marked acidosis rarely develops and, barring liver necrosis, a good recovery, with eventual healing of the skin defect, is accomplished.

Animals treated by moist dressings with tanning agents have a course more like the animals dressed with bland preparations except that necrosis and infection is somewhat reduced. With the bland dressings the injured

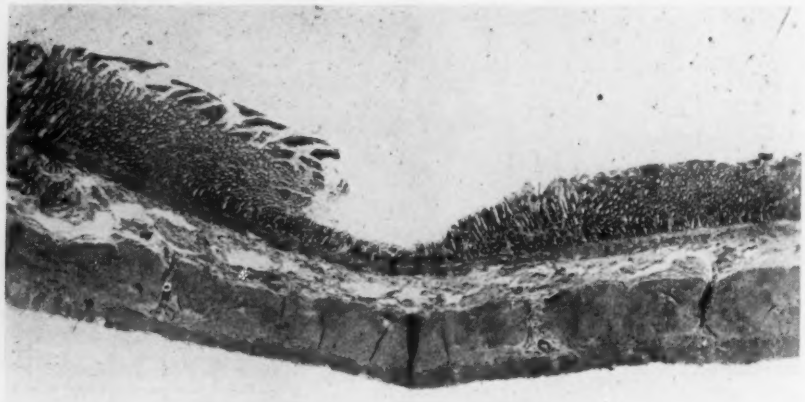

FIG. 11.—Dog No. 3208.—Photomicrograph showing smallest mucosal erosion, with no inflammatory reaction. (Low power)

tissue rapidly begins to undergo autolysis. This, coupled with great and continued loss of plasma into the dressings, favors extensive infection with the various types of organisms listed. The appetite is reduced, so that despite careful feeding there is marked weight loss; acidosis, septicemia, coma and convulsions are frequent. Loss of plasma, rapid autolysis of injured tissue with infection and acidosis are the factors found in this group which may logically be cited as the variables responsible for duodenal ulceration and death.

SUMMARY

1. Fifty animals had third degree burns of 50 to 60 per cent of the body surface produced and dressed with vaseline or similar preparations. Curling's ulcer was a complication in 32, or 63.3 per cent.

2. Thirty animals had third degree burns of 50 to 60 per cent of the body surface produced, and were dressed with tannic acid or other tanning agents. Curling's ulcer was a complication in two, or 6.6 per cent, and in these the dressing was of the wet type.

3. Loss of plasma, autolysis with infection, and acidosis occurring in the first group, with 57 per cent higher incidence of Curling's ulcers over the second group, suggest themselves as etiologic factors.

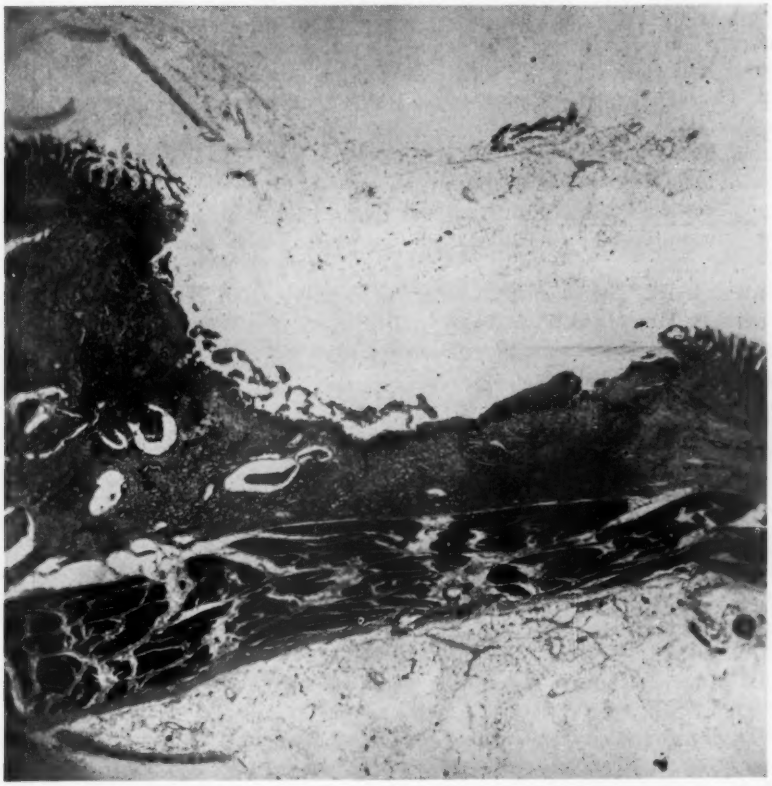

FIG. 12.—Dog No. 3099.—Photomicrograph showing thickened, infiltrated duodenal wall, with deep ulcer. (Low power)

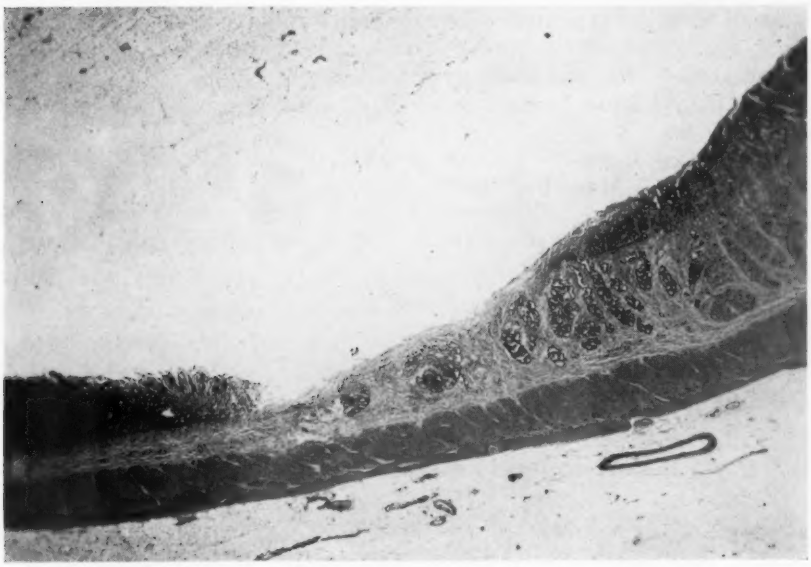

FIG. 13.—Dog. No. 3256.—Photomicrograph showing shallow ulcer extending to submucosa. (Low power)

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TRANSTHORACIC ESOPHAGOGASTROSTOMY FOR CARCINOMA OF THE MIDDLE THIRD OF THE ESOPHAGUS

REPORT OF A SUCCESSFUL RESECTION

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AT THE PRESENT TIME transthoracic resection for carcinoma of the lower third of the esophagus with esophagogastrostomy has become a well-standardized procedure which can be performed with considerable success.

Progress in the surgical treatment for carcinoma of the middle third of the esophagus has not kept pace with that of the lower third or with other thoracic tumors. Until recently all of the carcinomas of the middle third were resected by the method used and developed by Torek.[1] Although this procedure fulfills the principles of good cancer surgery it is not entirely satisfactory, in that esophagogastric continuity is not reestablished.

The cervical esophagostomy may be connected to the abdominal esophagostomy or gastrostomy by means of an anterior thoracic esophagoplasty or, if such is unsuccessful, a rubber tube. The rubber tube connection is an unending source of complaints. The tube frequently becomes dislodged or plugged and is almost constantly leaking. Many ingenious methods have been proposed for anterior thoracic esophagoplasty utilizing skin tubes (Bircher), stomach (Kirschner), gastric tube (Beck, Jianu), jejunum (Roux, Herzen), colon (Vulliet-Kelling), and a combination of jejunum and skin tube (Lexer, Wullstein). Most of these operations require multiple operative procedures and are quite difficult to perform. Yudin[2] has recently reported the construction of an artificial esophagus in 80 cases of stricture of the esophagus. In six of these he used Bircher's cutaneous tube method; 16 had a direct anastomosis performed between the pharynx and a jejunal transplant, and 58 were operated upon by the combined methods using a segment of jejunum for the lower part and a skin tube above.

Such procedures, as Yudin describes, may be applicable for a carcinomatous lesion in the upper third of the esophagus, but are certainly not ideal for neoplasms of the middle or lower third of the esophagus. If a one-stage procedure is used the patient would be subjected to an operation of tremendous magnitude. In a two-stage procedure the patient would have to undergo the risk of a major operation before it is determined if the lesion is operable. In addition, there is always the possibility of death of the jejunal transplant and/or infection of the subcutaneous tube.

Construction of skin tubes, either with or without jejunal transplantation, usually requires numerous operative procedures. Fistulae develop and strictures occur at the mucocutaneous junctions. Both of these distressing complications are difficult to handle. More than 50 per cent of

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anterior dermato-esophagoplasties are never completed, most of the patients dying of recurrence before the skin tube is completed.

Recently, Garlock[3] described a method for reestablishment of esophagogastric continuity after resection of a carcinoma of the middle third of the esophagus. In his case he anastomosed the fundus of the stomach over and above the arch of the aorta. This procedure is a definite advance in the surgical treatment of carcinoma of the middle third of the esophagus. It not only affords radical removal of the tumor, but eliminates artificial swallowing devices or anterior thoracic esophagoplasties.

The success of Garlock prompted the author to attempt a similar procedure in a man who had a carcinoma involving the middle and lower thirds of the esophagus.

FIG. 1.—Roentgenogram of esophagus following ingestion of barium showing an irregularly stenosing filling defect which begins at the level of the 6th thoracic vertebra and extends to the diaphragm.

Case Report.—P. P., white, male, age 58, was admitted to the University of Chicago Clinics January 17, 1944. About four and one-half months before, he had noticed the onset of difficulty in swallowing meat and coarse foods. This difficulty gradually progressed, and for about one month prior to admission he could only take liquids, and even these were taken with difficulty. Solid foods would regurgitate almost immediately. He had some cough for two weeks, but there had been no change in his voice. Saliva would seem to accumulate in the upper esophagus and then he would have to "cough it up." He had no pain, but there was a sensation of food "sticking" in his throat. He had lost 29 pounds in weight and had become quite weak. Past history is not significant.

Physical Examination.—The patient was a man of very small stature, somewhat emaciated, with evidence of recent weight loss. There were numerous carious teeth and marked pyorrhea. His voice was normal and he had no dyspnea. Lungs were clear. No cardiac murmurs. His blood pressure 102/70, pulse 75. Reflexes were equal and active.

Laboratory Data.—White blood count 11,100, with a normal differential, hemoglobin 13 Gm.; red blood count, 4,390,000. The urine was negative; blood chlorides 102.5 mM/L; fasting blood sugar 75 mg. per cent; plasma protein 6.38 Gm. per cent; N.P.N. 19 mg. per cent. Electrocardiogram was essentially normal.

Roentgenologic examination following ingestion of barium revealed an irregular filling defect, suggestive of malignancy, involving the lower two-thirds of the esophagus (Fig. 1). The chest showed no abnormalities.

At esophagoscopy, an ulcerating, friable mass, projecting into the lumen of the esophagus which bled easily, was seen. The lumen was considerably narrowed. A biopsy was made which subsequently revealed the lesion to be a squamous cell carcinoma.

Preoperative Preparation.—The patient was in the hospital for one week prior to the operation, during which time he was given a high protein, high caloric diet supplemented with vitamins. Five days before operation he received 600 cc. of whole citrated blood. He was slowly digitalized over a period of five days, and for four days before operation he received one gram of sulfadiazine four times per day.

Operation.—January 24, 1944: Positive pressure ethylene-oxygen-ether anesthesia, administered through a snug-fitting face mask was employed. The patient was placed on his right side with the left arm suspended from a rectangular frame (Fig. 2). A

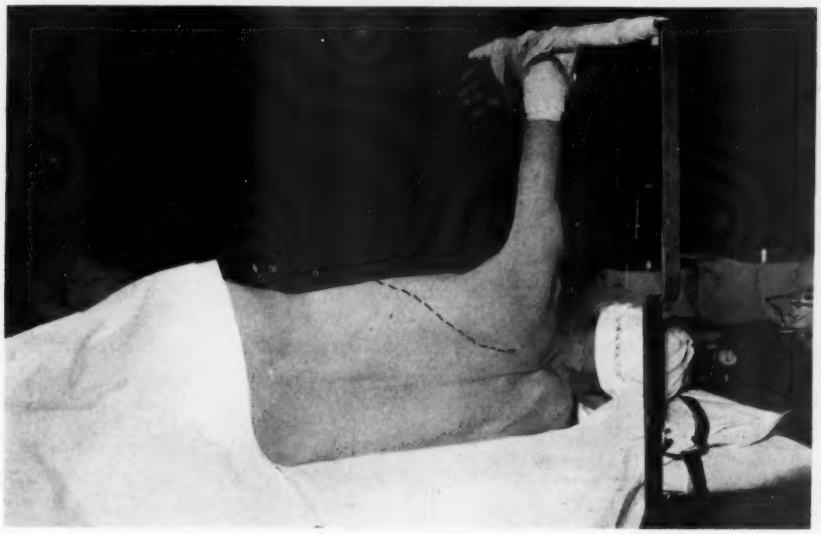

FIG. 2.—Photograph showing position of patient on the operating table. Dotted line indicates approximate skin incision.

long incision was made over the course of the seventh rib beginning at the costochondral junction anteriorly and extending backward to about the lateral edge of the recti spinae muscles. At this level it was carried upward for a distance of about 8 cm. (Fig. 2). The muscles were divided and the 7th rib exposed. At the posterior part of the wound the recti spinae muscles were reflected mesially exposing the posterior part of the rib and its accompanying transverse process. The entire rib was removed subperiosteally from its costochondral junction to the transverse process. The intercostal structures above and below the resected rib were divided between clamps near the transverse processes and ligated. The 6th and 8th ribs were transected about one inch from their accompanying transverse processes. The inner costal structures above and below these latter ribs were divided and the 5th and 9th ribs transected. This allowed the wound to be spread widely and afforded excellent exposure. The phrenic nerve was crushed just above the diaphragm. The esophagus, from just above the level of the arch of the aorta to just above the diaphragm, was involved in a very extensive neoplastic process. The mediastinal pleura was incised along the mesial edge of the aorta from the diaphragm to the arch of the aorta. By means of blunt and sharp dissection the esophagus was mobilized from the posterior mediastinum. This mobilization was begun just above the diaphragm and carried upward to the arch. Several adjacent firm, slightly enlarged lymph nodes were freed and left attached

to the esophagus. Both vagus nerves were divided above the diaphragm. As the lower portion of the esophagus was freed, a small opening was made in the opposite mediastinal pleura. This did not seem to cause the patient any particular difficulty but did require a slight increase in the intratracheal pressure. At the arch of the aorta the esophagus was intimately adherent to the adventitia, trachea and left main bronchus. The mediastinal pleura was incised above the arch to the suprasternal notch. The esophagus above the level of the tumor was easily freed. By careful blunt dissection the involved esophagus was freed from beneath the arch of the aorta and from the trachea and left main bronchus. A portion of the adventitia was left attached to the esophagus. A 16-cm. radial incision was made in the diaphragm from the periphery toward the esophageal hiatus. The left phrenic artery was divided and ligated. A mass of enlarged lymph nodes were found adherent to the left gastric artery near its origin. No other metastases could be seen or felt. The greater omentum was divided close to the stomach down to near the pylorus. This division was made so that the gastro-epiploic vessels remained in the omentum. The ligation was carried down to where the first branch of the right gastro-epiploic artery came off to the stomach. In order to remove the lymph node metastases it was necessary to divide the left gastric artery near the celiac axis. The upper and lower branches of the left gastric artery were divided and the gastrohepatic omentum incised near the liver. The lesser omentum, left gastric artery and its accompanying nodes were completely excised from the lesser curvature of the stomach. The stomach was divided just below the cardio-esophageal junction and the distal end infolded with two rows of linen sutures. The proximal end was covered with a rubber glove. The mobilized esophagus was then drawn out through the opening in the mediastinal pleura above and to the left of the arch of the aorta. The stomach, which appeared viable, was easily brought up into the chest and an anastomosis made between the end of the esophagus and an opening in the fundus of the stomach, with three rows of interrupted sutures of linen. The sutures were so placed that the esophagus was telescoped into the fundus of the stomach. The first posterior row of sutures was placed about 6 cm. above the upper limits of the tumor. An umbilical tape was placed around the esophagus 3 cm. above these sutures and tied twice, the second tie being a slipknot. The lower two-thirds of the esophagus was now removed and the anastomosis completed. There was no tension on the suture line. The elongated stomach was sutured to the pericardium and pleura over the aorta as far as the diaphragm which was closed with interrupted sutures around the prepyloric portion of the stomach (Fig. 3). Five grams of sulfathiazole crystals were sprinkled in the operative field. A de Pezzar catheter was inserted posterolaterally through the 9th interspace for pleural drainage. The wound was sutured tightly. The defect in the posterior aspect of the wound, which is always difficult to deal with, was adequately closed by using the reflected recti spinae muscles. The intratracheal positive pressure was increased and the air aspirated from the pleural cavity through the de Pezzar catheter. During the course of operation, which lasted six and one-quarter hours 2400 cc. of whole blood, 550 cc. of plasma and 1850 cc. of saline were administered. The patient stood the operative procedure very well.

Postoperative Course.—Immediately after operation the de Pezzar catheter was attached to a modified double Wangensteen suction apparatus[4] and nasal oxygen started. The patient got along very well for six days, and liquids by mouth were started on the seventh day. He received 5 Gm. of sodium sulfadiazine intravenously and one cat-unit of digitalis intramuscularly daily. His temperature rose to 101° F. on the second day and then gradually fell to normal by the sixth postoperative day. On the seventh day he became quite dyspneic, and examination revealed fluid in the right chest. Thoracentesis was performed and 2000 cc. of chylous-appearing fluid was removed.

Cultures of the fluid were sterile, protein content 3.25 Gm. per cent, total lipids 500 mg. per cent. Following this, his dyspnea entirely disappeared, and he felt quite well. 2700 cc. of similar fluid was removed from the chest on the following day. This, likewise proved to be sterile and had about the same protein content. On this day he was given 1100 cc. of plasma to replace the protein loss in the fluid. On the ninth day he again showed signs of fluid accumulation in the chest and 1800 cc. of chylous-appearing fluid was removed. This was given back to him intravenously without reaction. On the tenth day 440 cc. of fluid were aspirated from the right chest and on this day the administration of sulfadiazine and digitalis were discontinued. By the eleventh day he was feeling fairly well and taking soft foods by mouth. He took food without difficulty in the upright position but when he was lying down he would choke, which was apparently due to accumulations in the thoracic stomach. He had a fairly good appetite and apparently had hunger pains. He was discharged on his twenty-seventh postoperative day.

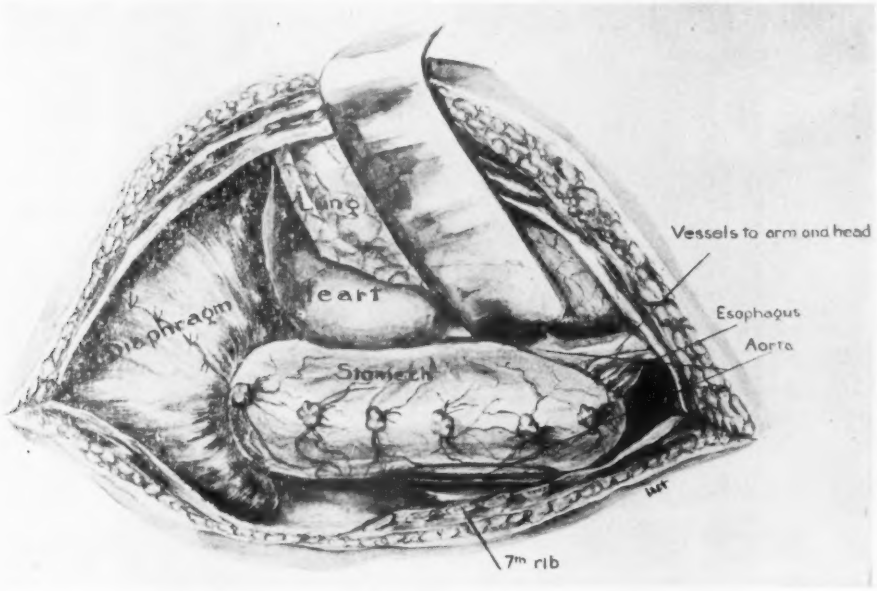

FIG. 3.—Shows the diaphragm closed around the prepyloric region and the elongated stomach anastomosed to the esophagus above the aortic arch. The stomach is drawn over the aorta.

An electrocardiogram taken ten days before his discharge showed no significant change from the preoperative tracing. Histamine test done three and one-half weeks postoperatively showed 78 clinical units of free hydrochloric acid in the 30-minute specimen. Roentgenologic examination after barium swallow, made two and one-half weeks postoperatively, revealed nearly all of the stomach in thorax and a well-functioning esophagogastrostomy (Fig. 4).

The patient got along quite well for three and one-half months, then he began to lose weight and strength. A cough developed and his appetite failed. His condition gradually became worse, and he died June 23, 1944. Autopsy was not permitted.

Pathologic Report.—Microscopic examination of the esophagus showed the lesion to be a squamous cell carcinoma. The mass of tissue removed from the lesser curvature of the stomach contained eight lymph nodes. Seven of these showed invasion of neoplastic cells.

DISCUSSION.—Progress in esophageal surgery has not only been due to a better understanding of the physiology of the cardiorespiratory system, but also to improved pre- and postoperative care. Most of the patients when seen with neoplasms of the esophagus are elderly, dehydrated and undernourished. Restoration of fluid and electrolyte balance as well as plasma protein level should be routine preoperative procedures.

FIG. 4.—Roentgenogram of esophagus and stomach following ingestion of barium, two and one-half weeks after resection and esophagogastrostomy. It shows nearly all of the stomach in the thorax. The anastomosis is at the level of the clavicles and the diaphragm is closed around the prepyloric region of the stomach. Fluoroscopy revealed no evidence of obstruction at this time.

Many of the patients who have been subjected to surgery of the esophagus have been given digitalis preoperatively. Although one cannot determine definitely when full digitalization has been accomplished we have administered an amount calculated on the basis of body weight. No adverse reactions have been observed, and the incidence of cardiorespiratory complications have been less in the cases where preoperative digitalization has been carried out. Garlock, in his case, divided only the upper branch of the left gastric artery.

He believed that if the main vessel was ligated the blood supply of the upper end of the stomach might be too seriously jeopardized. In the case reported herewith the greater and lesser curvatures were ligated off, down to the prepyloric region leaving only the blood supply which comes from the prepyloric segments of the right gastric and right gastro-epiploic arteries. Despite this extensive sacrifice of blood vessels the circulation of the stomach remained adequate.

FIG. 5.—Photograph of the resected specimen of esophagus. Note the extent of the lesion.

Ligation of the blood supply to such an extent presumably may result in necrosis of the stomach in some cases. Therefore, a safer procedure would be to leave the right and left gastro-epiploic vessels attached to the stomach, as shown in Figure 6, dividing and ligating the omentum distally. If this were done complete removal of the left gastric artery and its accompanying nodes could be performed with very little fear of impairment of gastric circulation. Since the lymph nodes along the lesser curvature of the stomach

are intimately associated with the lymphatic drainage of the esophagus, and usually contain metastases, their removal is absolutely indicated.

For three and one-half months following operation the patient had very little trouble taking solid food providing he would eat in an upright position. Shortly after he began to lose his appetite he noticed that if he ate a moderate amount of food a sense of fullness would develop in the lower chest and epigastrium. He had some vomiting which gave relief. Roentgenologic study after the ingestion of barium, made at this time, revealed a marked

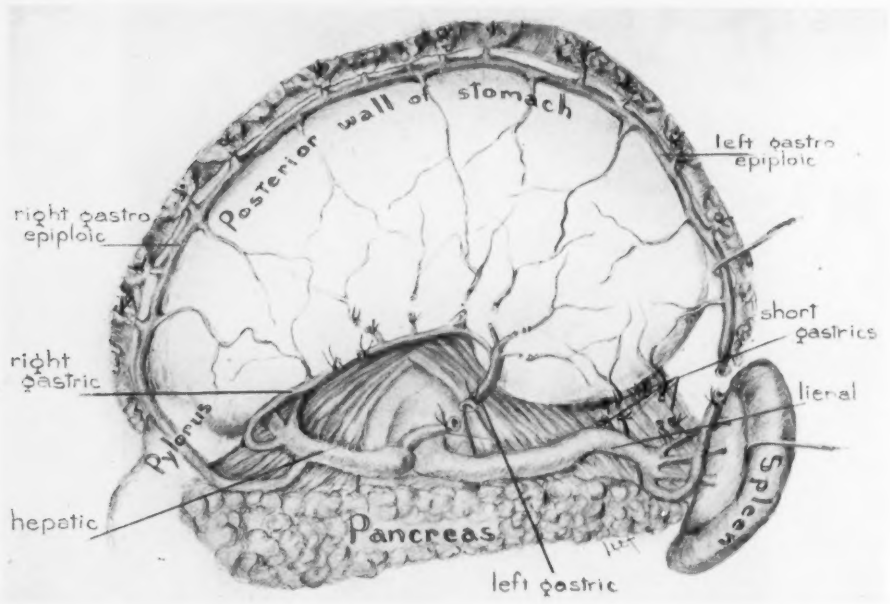

FIG. 6.—Diagram of the blood supply to the stomach, indicating points of ligation of the vessels which would allow complete removal of the lymph nodes along the lesser curvature of stomach without fear of impairment of gastric circulation. The right and left gastro-epiploic vessels are left attached to the stomach dividing and ligating the omentum distally. In the case presented the greater and lesser curvatures were ligated off down to the prepyloric region leaving only the blood supply which comes from the prepyloric segments of the right gastric and right gastro-epiploic arteries.

obstruction of the stomach where it passed through the diaphragm. The excursion of the left leaf of the diaphragm was full. It appeared that the obstruction was due to regeneration of the phrenic nerve and recovery of the muscle tone of the diaphragm. In view of this, it is a question if it would not be better to excise a long segment of the phrenic nerve to insure permanent paralysis of the left leaf of the diaphragm. Many of the patients in whom part of the stomach has been transplanted into the chest complain of vague symptoms not unlike those of patients with diaphragmatic herniae. Permanent paralysis of the diaphragm may relieve or prevent many of these symptoms.

The patient's postoperative course was complicated by a chylous thorax. Because of the anatomic location of the thoracic duct, the injury of it may be more frequent in resecting lesions of the middle third of the esophagus

than in operations for lesions of the lower third. This complication has been observed now in two cases in this clinic. In both, the accumulation of chyle ceased spontaneously in three to four days. Since the protein content of chyle is about 2–4 grams per cent, depletion of the protein stores will occur very rapidly unless adequate replacement is promptly instituted. Plasma should be given or the chylous fluid, if sterile, may be administered intravenously. In the case reported, 4700 cc. of milky fluid, with a protein content of 3.25 Gm. per cent, was removed from the right chest on the seventh and eighth postoperative days. This protein loss was partially covered by the administration of 1100 cc. of plasma. On the ninth day 1800 cc. of similar fluid was obtained which was immediately administered intravenously, without any reaction.

Operations, such as the one described, are of tremendous magnitude, and the loss of blood is considerable in spite of careful hemostasis. If adequate blood and/or plasma replacement is carried out during the course of the operation the patients usually stand the procedure very well. Although this patient was a small man he was given 2400 cc. of whole citrated blood and 550 cc. of plasma during the operative procedure. There was no evidence of reaction from the citrate administered in the blood and plasma.

SUMMARY

1. A successful resection of a carcinoma of the middle third of the esophagus is reported. The esophagogastric continuity was reestablished by an anastomosis between the stomach and esophagus over and above the arch of the aorta.

2. A technic is suggested for preservation of the gastro-epiploic arteries which would allow complete removal of the left gastric artery and the lymph nodes along the lesser curvature of the stomach without fear of impairment of gastric circulation.

3. Certain aspects of the pre- and postoperative treatment are discussed.

4. Excision of a long segment of the phrenic nerve is recommended to insure permanent paralysis of the diaphragm.

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THE EFFECT OF CHEMOTHERAPY ON THE ILEUM SUBJECTED TO VASCULAR INJURY

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THE EXTENT to which intestinal flora aggravate the damage to the intestine inflicted by vascular injury has not been clearly demonstrated. The recent introduction of potent intestinal antiseptics,[1-7] succinylsulfathiazole and pthalysulfathiazole in particular, has made it possible to undertake such a study.

In a preliminary study Sarnoff and Poth[8] found that succinylsulfathiazole conferred a protective effect upon a 50-cm. segment of ileum with occluded venous return, by preventing perforation and permitting recovery of bowel integrity. In this report data is presented demonstrating the usefulness of chemotherapy in experimental venous obstruction and in strangulation obstruction of the ileum of the dog.

METHOD

In the morphinized dog under ether anesthesia a 50-cm. loop of terminal ileum is exposed through an abdominal incision, with aseptic precautions. The accompanying mesentery is freed from adjacent mesentery by incision along its entire length from bowel to root of mesentery without injury to the vessels serving the rest of the intestine. All the veins in the isolated mesentery, which can be identified, are divided between ligatures. The division of the mesentery adjacent to the ends of the loop is carried to intestinal serosa, so that no identifiable vascular communication with adjacent loops remains. The incision is closed (Fig. 1).

One series of dogs, Group I A, so treated, received no preoperative chemotherapy. Another, Group I B, received preoperative chemotherapy as follows: Of 16 dogs, seven received 0.5 Gm./Kg. of succinylsulfathiazole daily in their food or by gavage,* and nine received 1.0 Gm./Kg. of succinylsulfathiazole daily by gavage. Water was allowed postoperatively but food was withheld for 48 hours. All blood specimens were taken from the femoral artery. Hematocrit, plasma volume and plasma protein concentration were obtained immediately prior to venous occlusion and again 24 hours later.

The plasma volume was determined by the methods of Gibson and Evelyn,[9] and of Gregerson and Gibson,[10] using the photo-electric colorimeter. Plasma protein concentration was determined from the plasma specific gravity (pycnometry method of Phillips, *et al.*[11]), and the conversion formula of Weech, *et al.*[12]

* Three of these also received the drug in the same dose by gavage or in their food for two weeks postoperatively.

Autopsy was performed immediately after death or, in the case of surviving animals, after they were sacrificed at varying intervals postoperatively. Evidence was obtained on the source of collateral venous supply in the surviving animals and sections were taken for microscopic study.

When the venous return of a loop of ileum is treated as described, the following changes are observed. After five minutes cyanosis is obvious,

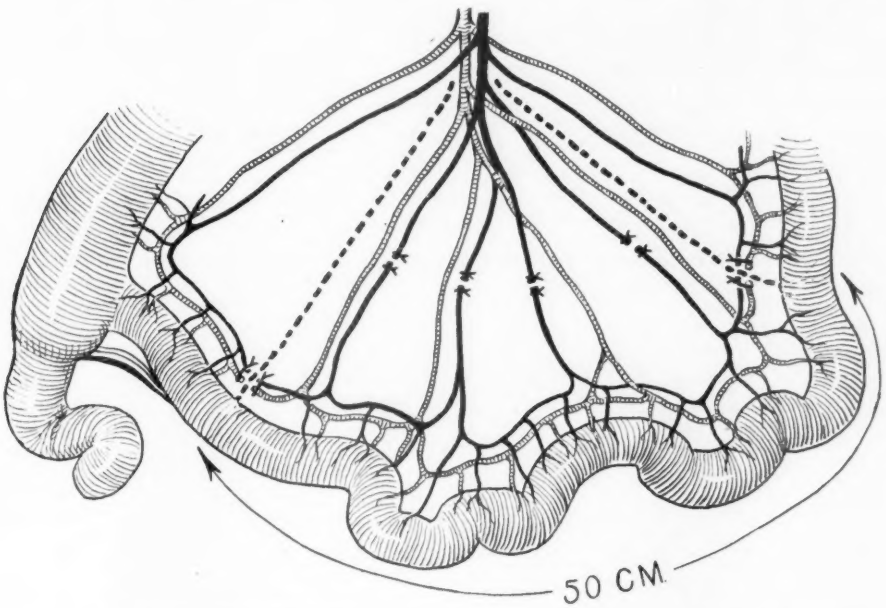

FIG. 1.—Schematic diagram indicating procedure for occlusion of venous return of ileum.

and after 15 minutes arterial pulsations disappear and the distended veins have pressures approaching the arterial diastolic pressure. After two hours the loop is deep purple, swollen and juicy, and the mesentery shows extravasation of blood as far proximally as the ligatures on the veins. The volume flow through such a loop approaches zero since, if exteriorized, the temperature of the loop approaches that of the environment, while adjacent loops are near body temperature.

In a second group of dogs, the foregoing procedure was repeated but the chemotherapy applied was as follows: Nine (Group II A) received succinylsulfathiazole locally (1.0 Gm./Kg.), introduced at the time of operation by needle and syringe into the lumen just proximal to the loop and gently distributed in the area. No other chemotherapy was administered. In eight others, Group II B, the only chemotherapy administered was sodium sulfathiazole intravenously (0.1 Gm./Kg.) immediately postoperatively and 0.05 Gm./Kg. twice daily for one to two days thereafter.

In a third group (III) of 17 dogs, under evipal anesthesia, strangulation obstruction of a 35-cm. loop of terminal ileum, exposed under aseptic precautions through an abdominal incision, was produced by tying a rubber

FIG. 2.—A. Gross appearance of cross-section of ileum after 24 hours of occlusion of venous return of ileum. No chemotherapy.

FIG. 2.—B. Gross appearance of cross-section of ileum after 24 hours of occlusion of venous return of ileum. Succinylsulfathiazole by mouth for ten days prior of venous occlusion.

band around the base of the loop so as to produce venous obstruction, as evidenced by cyanosis, without occluding arterial flow. Twelve to fourteen hours later the incision was opened, under light ether anesthesia, and the rubber band released. Many of the dogs, of course, showed evidence of shock. All had copious bloody peritoneal fluid. Nine dogs were treated immediately thereafter by an infusion of 5%-7% gelatin, in a volume equivalent to 60% of the dog's calculated blood volume. The remainder were treated likewise, but they also received chemotherapy as follows: One Gm./Kg. of succinylsulfathiazole by syringe and needle into the loop proximal to the released loop and the same amount by mouth daily for two days thereafter; in addition sodium sulfathiazole 0.1 Gm./Kg. was given in the gelatin infusion and 0.05 Gm./Kg. intravenously twice daily for two days thereafter.

TABLE I

SURVIVAL TIME FOLLOWING VENOUS OCCLUSION OF 50-CM. LOOP OF TERMINAL ILEUM

Control Group			Treated Group (see text)		
Dog No.	Survival Time in Hours	Sacrificed Days Postoper.	Dog No.	Survival Time in Hours	Sacrificed Days Postoper.
1	47	..	1	..	15
2	..	23	2	..	22
3	40	..	3	42	..
4	..	13	4	..	30
5	42	..	5	..	60
6	42	..	6	..	3
7	36	..	7	..	10
8	39	..	8	43	..
9	84	..	9	..	6
10	..	10	10	24	..
11	20	..	11	..	51
12	38	..	12	..	51
13	6.5 days	..	13	..	51
14	35	..	14	..	30
15	45	..	15	48	..
16	37	..	16	..	30
17	37	..			
18	35	..			
19	12	..			
20	34	..			
21	30	..			
22	20	..			
23	40	..			
	Average wt. = 9.5 Kg.	Mortality 87%		Average wt. = 9.3 Kg.	Mortality 25%

RESULTS

Group I (Table I): Venous Occlusion With Preoperative Peroral Chemotherapy.

In this group of dogs, with simple venous occlusion of a loop of ileum, 23 untreated control dogs (Group I A) showed a mortality of 87 per cent, death occurring in all but two of these dogs in less than 47 hours. The group of 16 dogs receiving chemotherapy (Group I B), showed a mortality of 25 per cent within 48 hours. The remainder survived, and were sacrificed at intervals varying from 3-60 days postoperatively. The surviving dogs lost weight, but appeared reasonably well and took food from the second postoperative day.

In Table II data on changes during the first 24 hours postoperatively in blood and plasma volume, hematocrit and plasma proteins are listed. It is clear that no significant alterations occurred in these categories in both the treated and untreated groups of dogs. Therefore, when death occurred, it could not be attributed to shock resulting from blood loss arising from the vascular damage. The autopsy findings demonstrate that in the untreated group (I A) death was due to partial or complete dissolution of the loop, with resulting peritonitis. The four treated dogs which died differed from the untreated dogs in that no perforation was present. Nevertheless two showed gross evidence of peritonitis.

TABLE II

BLOOD CHANGES 24 HOURS AFTER VENOUS OCCLUSION OF ILEAL LOOP

Dog No.	Blood Volume % Change	Plasma Volume % Change	Hematocrit % Change	Plasma Proteins % Change	Survival Time Hrs.
Control					
8	−11.8	+ 6.4	− 9.5	−10.0	39
9	−20.5	−22.8	− 2.3	−15.0	84
10	− 6.0	− 3.0	− 1.8	−13.9	s‡
12	−23.6	−31.7	+ 5.2	+ 3.0	38
23	− 4.8	−10.5	+ 3.0	0	40
Average	−13.3	−12.3	− 1.1	−17.2	—
Treated					
5	− 4.8	−12.2	+ 4.0	− 8.5	s‡
6	−12.8	0	− 6.5	− 8.0	s‡
7	−10.5	− 7.0	− 2.1	− 7.8	s‡
8	−27.7	−17.5	− 8.4	−11.1	43
9	−18.5	−14.4	− 2.8	− 8.0	s‡
1†	−29.5	−26.7	− 1.4	0	s‡
2†	−25.2	−23.4	− 2.5	− 7.2	s‡
3†	−11.3	+ 3.0	− 7.0	−16.7	42
4†	−18.7	−21.7	+ 1.5	− 1.3	s‡
Average	−14.9*	−10.2	− 3.2	− 8.8	

‡s = Survived until sacrificed.

† Preoperative blood volume estimated as 10% of the dog's weight in kilograms. Preoperative plasma volume calculated from preoperative blood volume and hematocrit.

* Calculated for Dogs 5–9, inclusive.

Examination of the loops from surviving animals showed that venous collateral supply to the damaged segment was provided from three sources:

(a). The omentum, which was usually found adherent to the damaged segment.

(b). The mesentery of the damaged loop showed numerous functioning venous channels, evidently submacroscopic vessels, not detectable in the mesentery at the time of venous occlusion, which had become dilated.

(c) Adherent neighboring loops of bowel which oozed freely when separated. Gross inspection of the damaged loops at the time of sacrifice showed slight mottling, a somewhat larger luminal diameter, less active peristalsis than adjacent loops. The mucous membrane was intact and the mesentery showed some fibrosis.

Sections for microscopic study were taken at varying intervals after

operation in the treated group. Examination of these sections yielded the following information:

Twenty-four hours after operation: Ulcerative necrosis of the mucosa with polymorphonuclear infiltration. Tissue from submucosa to serosa hemorrhagic but relatively intact. Process of repair evident in deep portion of mucosa and in muscularis. Lymphatics distended. Arteries contracted. No bacteria seen.

Three days after operation: Massive hemorrhage into the mesentery, the entire muscularis and between mucosal glands and mucularis mucosae. Superficial portion of the villi edematous. In places superficial necrosis of the mucosa and replacement with granulation tissue. Fibrin deposits on the serosa. Almost complete absence of thrombosis.

Six days after operation: Hemorrhage into mesentery and the muscularis. Fibroblasts and lymphocytic infiltration of the mesentery and submucosa. The venules and capillaries of the submucosa distended. Extensive slough of mucosa with granulation tissue replacement. Fibrin deposits on thickened serosa. No evidence of thrombosis.

Ten days after operation: Fibrosis, and lymphocytic infiltration of the mesentery, thickening and lymphocytic infiltration of serosa. The mucosa, submucosa and muscularis are not remarkable.

Twenty-two days after operation: Lymphocytic infiltration of mesentery. Occasional organized mural thrombus in mesenteric veins. Intestine otherwise normal.

Thirty days after operation: Except for some thickening of the serosa at the site of adhesions and some fibrosis in the mesentery, tissue is indistinguishable from normal bowel.

TABLE III

EFFECT OF CHEMOTHERAPY ON MORTALITY AND PERFORATION FOLLOWING VENOUS OCCLUSION OF A 50-CM. LOOP OF ILEUM

	Group	No. of Dogs*	Mortality Rate	Perforation Rate in Animals that Died
I A	No chemotherapy	23	87%	75%
II A	Intraluminal chemotherapy at time of venous occlusion (succinylsulfathiazole)	9	66%	0
II B	Intravenous chemotherapy for 24–48 hours following venous occlusion (sodium sulfathiazole)	8	50%	0
I B	Preoperative chemotherapy (succinylsulfathiazole)	16	25%	0

* Average weight in different series: 9.3 – 10.4 Kg.

Group II: Venous Occlusion With Simultaneous Chemotherapy.

(A) *Local Instillation of Succinylsulfathiazole:* Of nine dogs in this group (II A, Table III) six succumbed in under 48 hours. There were no perforations, however, in any of these six animals, although in two the wall was quite thin and gross peritonitis was present. The remaining three survived, and showed the gross findings already described for survivors in Group I B.

(B) *Intravenous Sodium Sulfathiazole:* Of eight dogs (Group II B, Table III), which received intravenous therapy as described, four died, but, as in the locally treated group, no perforations were present. The remaining four survived and showed, when sacrificed, the usual findings seen in surviving animals.

Group III: Strangulation Obstruction.

Of nine dogs with strangulation obstruction (released after 12-14 hours) which received an adequate volume of a blood substitute (gelatin) but no chemotherapy, none survived, death occurring from gangrene of the loop and diffuse peritonitis. Survival was less than 20 hours after release of the strangulation in all but two, which survived six days. In the latter two, autopsy showed peritonitis but no obvious perforations; the remainder showed perforations.

Of a similar series of nine dogs, which received chemotherapy as described, three survived and six died. Two of the six which died showed perforations and peritonitis at autopsy; a third showed peritonitis too but no perforation, the loop having apparently recovered; two more showed no perforation but gangrene was present, while the sixth showed neither, and died of bilateral pneumonia. Of the nine treated dogs, therefore, the chemotherapy prevented death in three, perforations in seven and peritonitis in five. The survival time in the five which died was 2, 4, 4, 2 and 5 days as compared to an average of 20 hours for the dogs not receiving sulfonamides. The three surviving dogs showed a remarkable degree of recovery of the loop. All layers of the intestine showed a somewhat dusky, deep brownish-red discoloration; there was slight edema of the mucosa, which, however, was intact throughout. The mesentery was slightly cloudy and thickened, and the serosal surface of the intestine showed patches of fibrin in addition to easily separated adhesions between adjacent surfaces. The only evidence of ileus was very slight dilatation of the proximal intestine in a few of the dogs. The vascular supply to the loop was apparently normal by gross inspection.

In view of the fact that the loop in 87 per cent of the dogs not receiving sulfonamides showed partial to complete necrosis, the protective effect of chemotherapy is obvious.

Discussion.—Numerous quantitative studies[13, 14] have demonstrated that severe vascular damage to the intestine can be rapidly fatal from loss of blood volume alone. For the clinical surgeon, the therapeutic problem, therefore, is made somewhat less difficult by the provision of blood volume replacement. But the primary lethal factor of secondary infection through a permeable bowel wall remains, so that resection not only of devitalized but of questionably viable loops constitutes a cardinal principle in the surgical treatment of strangulation and of mesenteric thrombosis.

The remarkable feature of sulfonamide action in the experiments de-

scribed is their apparent ability to forestall complete necrosis. Presumably, they do so by suppressing the thrombotic action of tissue juices or bacterial products in an area of threatened devitalization and so allow time for effective collateral supply to become established. The microscopic evidence in surviving animals is that remarkably little thrombosis is evident in the obstructed veins, whereas in the one microscopic section of an early stage in the rapid disintegration of a loop in an untreated dog, thrombosis of the veins was widespread.

There is no evidence to assume that the protective effect of the sulfonamides in these experiments is achieved by any other mechanism, *e.g.*, one which might directly or indirectly prevent a substantial fall in blood volume. No significant fall in blood or plasma volume was observed in treated or untreated dogs with simple venous occlusion, while in strangulation obstruction the loss in blood volume was adequately replaced in the treated and untreated series. Advance chemotherapy might have provided for more protection than was obtained in these strangulation experiments. But while such data should be secured, they have little practical bearing on the clinical problem of strangulation, since it is not a condition that can be anticipated.

The foregoing experiments suggest the potentialities of sufonamide therapy. The maximal effect possible with the relatively insoluble sulfonamides can be secured in elective bowel surgery. Since they require at least several days to produce a substantial bacterial depopulation of the intestine, their administration would not be appropriate in acute conditions in which vascular damage is already present, unless peritonitis may be anticipated; *e.g.*, in incomplete, but diffuse, mesenteric thrombosis, in which viability is problematical and in which resection is not advisable because of too extensive involvement of the intestine. The soluble sulfonamides have a certain limited usefulness at, and subsequent to, the time of operation for a strangulation, which is released but not resected, as the experiments of Groups II and III indicate, since perforation is frequently avoided by their use. Their administration in conjunction with the local instillation of the less soluble sulfonamides may be of not inconsiderable value in elective bowel surgery. For if a point in a suture line becomes partially devitalized because of a technical error or an unavoidable postoperative complication, the threat of peritonitis may be forestalled if bacterial permeation is kept to a minimum by these agents.

CONCLUSIONS

1. The lethal effect of the simple vascular occlusion produced in these experiments is not attributable to a crucial fall in blood volume, but to peritonitis with, or without, gross perforation.

2. The protective effect of succinylsulfathiazole is maximal when applied well in advance of production of the vascular injury, while chemotherapy at

the time of, or subsequent to, the production of the vascular injury is also effective but to a distinctly lesser extent than advance chemotherapy.

3. The data suggests the probable usefulness of chemotherapy in corresponding clinical states in man.

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DIVERTICULITIS OF THE CECUM: A METHOD OF MANAGEMENT

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DIVERTICULITIS OF THE CECUM is rarely included in discussions of diverticulitis of the colon since the former is characteristically solitary and appears to be a distinct entity. In recent years the subject has received considerable space in the literature. Schnug,[1] in 1943, reviewed 31 cases and added six of his own. In 1938, Bennett-Jones[2] had been able to collect but 19 cases to which he added three.

Most cases of diverticulitis of the cecum occur before the age of forty, and one-third of the cases have had previous attacks. Almost invariably, the preoperative diagnosis is acute appendicitis. Rarely is the diagnosis of diverticulitis made before celiotomy.[1]

At operation one may encounter a pericecal mass which is recognized as inflammatory, and palpation through the opposite cecal wall may reveal the mouth of a diverticulum. Often an inflamed or gangrenous diverticulum is obvious. Sometimes, the pathologic process becomes so tumefied and involved with enlarged mesenteric lymph nodes that the surgeon thinks he is dealing with a malignant tumor.

From the reviews,[1, 2] and from the case reports,[3, 4, 5, 6] it is evident that agreement as to the most satisfactory surgical approach has not been reached. Schnug advised chemotherapy without attempt at resection, on the basis of the tendency for the lesion to drain into the bowel and subside. Jonas reports that it has been their practice to resect the entire right colon and cecum with an ileo-transverse colostomy. Others recommend conservative surgery from simple drainage to local excision of the diverticulum and closure of the cecum.

The edema and thickening of the surrounding cecal wall make local excision of the diverticulum difficult and closure hazardous. This is true whether the diverticulum be mildly inflamed or strangulated, and with or without an attached inflammatory mass or abscess. To resect a large segment of the bowel for so benign a lesion seems most radical. On the other hand, to close the abdomen without attempting to eradicate the lesion and thus chance perforation challenges one's courage.

Case Report.—Hosp. No. 28696: Age 37. The patient was well until the day before admission when he experienced epigastric discomfort which later shifted to the right lower quadrant. There was no nausea, vomiting or diarrhea. On the morning of admission, the pain was more severe and was accompanied by anorexia. On physical examination, there was moderate tenderness in the right lower quadrant, maximum to the right of McBurney's point. A minimal amount of muscle spasm was present, and upon hyperextension of the right thigh, the abdominal tenderness became more pronounced. Rectal tenderness was absent. The leukocyte count was 12,800, with 77 per cent polymorphonuclears, 19 per cent lymphocytes and 4 per cent monocytes. Hemo-

globin was 14 Gm. The uranalysis was negative. *Clinical Diagnosis:* Acute appendicitis, probably retrocecal in position.

Operation.—Under spinal procaine anesthesia, later supplemented by intravenous sodium pentothal, the abdomen was opened through a conventional McBurney incision. A mass was felt in the posterior wall of the cecum which, after delivery into the wound, had the appearance of a neoplasm, incorporated in the cecal wall (Fig. 1). No crater was felt by palpation through the wall of the cecum. The serosa was divided and dissected off the tumor to its periphery where it appeared to diffuse with edematous

FIG. 1.—Schematic drawing of iliocecal region indicating the relative size and position of tumor of cecum.

cecum (Fig. 2 A). An incision was made into the tumor for biopsy, and upon incising for a depth of about seven millimeters a firm black mass was encountered (Fig 2 B). The hard shell was further incised and dissected from the new structure, which, when completely exposed, appeared as a gangrenous mass surrounded at its base by normal mucosa (Fig. 3 A). It was then apparent that the mass was a strangulated diverticulum. The granulomatous tissue, covering the diverticulum, was cut away, and the peritoneum was sutured to the serosa and thickened wall of cecum around the diverticulum (Fig. 3 B). The remainder of the wound was packed with vaselined gauze and, thus, the diverticulum was exteriorized.

Fecal material began to drain from the wound on the third day, and the patient's condition was good throughout a relatively uneventful convalescence. Two weeks

after operation he began to have formed stools per rectum. However, drainage from the wound persisted for a prolonged period, presumably due to the inflammatory state of the cecum. Barium enema showed a persistent small fistula, but otherwise, a normal colon without deformity of the cecum. Slight soiling of the dressing is still present at the time of this report, 45 days after operation.

DISCUSSION.—The mass encountered was incorporated in the wall of the cecum and covered by normal serosa (Fig. 1). There was striking absence

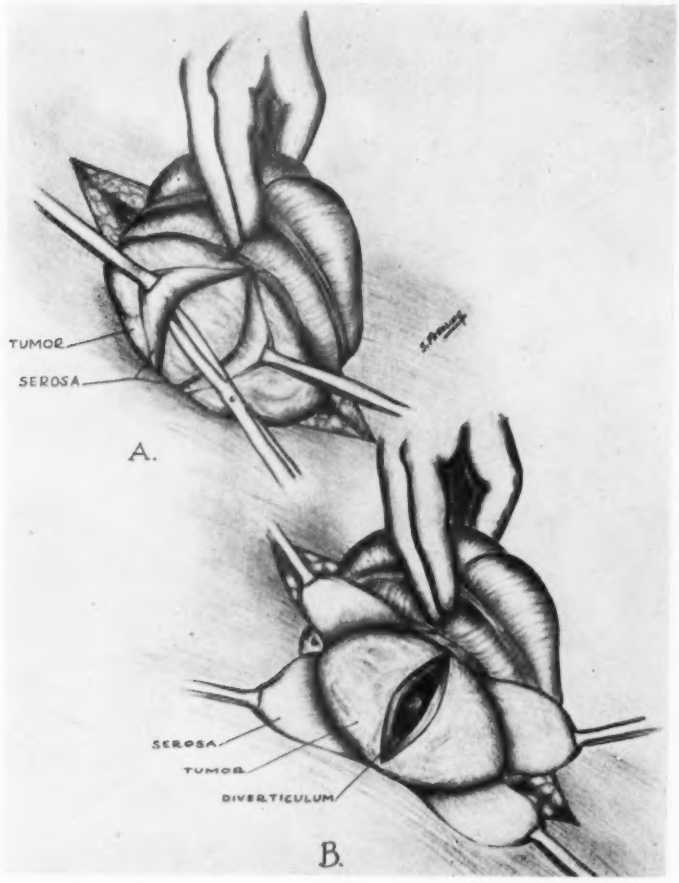

FIG. 2.—A. Showing cecum delivered and serosal covering of tumor being stripped away. B. Serosa has been stripped to periphery of tumor. Incision into substance of tumor reveals trapped diverticulum.

of any inflammatory adhesions. The tumor had the gross characteristics of neoplasm, and a Mikulicz resection was contemplated until the diverticulum was actually exposed during the procedure of securing a biopsy of the tumor.

It would have been impossible to excise the lesion without removing an excessive amount of colon. The large portion of cecum which made up the mass was greatly thickened and hard (Figs. 2 and 3), and the remaining cecal wall was edematous.

To leave a gangrenous diverticulum, particularly after it had been exposed, would violate the principles of good surgical judgment. Subsequent perforation would be disastrous. Extraperitonealizing the immediate site of the diverticulum, thus sealing the peritoneum around its base, assures an uncomplicated cecostomy. In 48 to 72 hours the gangrenous diverticulum will slough or can be opened very simply.

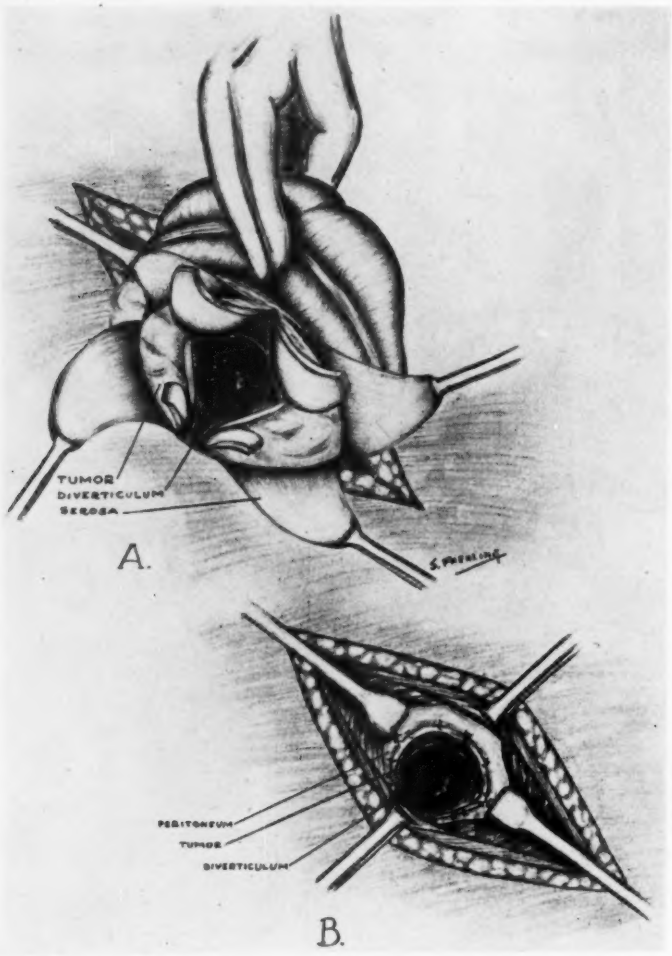

FIG. 3.—A. Incision into tumor extended and granulomatous wall dissected away from diverticulum. Normal mucosa surrounds base of diverticulum. B. The granulomatous wall has been cut away, and the cecum returned to the peritoneal cavity. The peritoneum has been sutured to the granulomatous wall of cecum around base of diverticulum.

In the absence of obstruction, the fistula should close spontaneously. The time required for this will undoubtedly depend upon the amount of inflammatory thickening of the cecum. It is possible that occasionally secondary closure of the cecum will be necessary.

It seems that the procedure described is applicable to most instances of

diverticulitis of the cecum, unless perforation and abscess formation have taken place. Obviously, these cases should be drained.

SUMMARY

1. The diverticula of the cecum are characteristically solitary.

2. At operation, many are mistaken for a malignant tumor of the cecum because of accompanying inflammatory mass.

3. The literature on the subject displays a variance of opinion as to the best surgical approach.

4. A case is presented, and illustrated, to demonstrate the difficulty in recognizing the pathology and the corrective procedure employed.

5. Extraperitonealization of the immediate site of the lesion as a prececostomy is suggested as the ideal method of management in most cases of solitary diverticulitis of the cecum.

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MULTIPLE POLYPOID DISEASE OF THE COLON AND RECTUM

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THE EXTRAORDINARY CONDITION variously termed by different writers polyposis, polypoidosis, multiple adenomatosis or multiple polypoid disease of the colon is a malady *sui generis*, and is distinctly different from cases of single or multiple polypi resulting from irritative or infective influences.

Virchow,[1] in 1863, first described this curious and rare disease, and, in 1882, Harrison Cripps[2] reported a case. All of the literature since the publication of the latter until 1930 was reviewed by Cuthbert Dukes[3] in the Cancer Review for April, 1930. During the intervening years to date, reports of single or small series of cases have appeared in the literature from time to time. In 1942, C. W. Mayo[4] reported that in postmortems of 334 patients who had died of primary carcinoma of the colon or rectum, eight showed multiple polypi. The senior author saw only two such cases on the rectal and colon service at the U. S. Naval Hospital, Philadelphia, during a three-year tour of duty, 1937-1940. One of these patients had developed two separate and distinct malignancies in his colon prior to the time of his reporting to the hospital. The junior author has seen two cases of heredofamilial multiple polypoid disease in his private work—a mother, age 60, and her daughter, age 25, both of whom died of extensive carcinomatosis. Buie,[5] in reviewing his series of 1234 cases of polypoid disease seen over a nine-year period, that is, 1925-1934, broke this series down into three groups as follows:

Group I: One or only a few polypi—1069.
Group II: Multiple polypi associated with inflammatory disease of the colon—110.
Group III: Multiple polypoid disease of the entire colon—55 (or 4 per cent of the entire series).

McLaughlin,[6] in 1943, stated that 331 cases had been reported in the literature since Virchow's original report in 1863.

The disease, although occurring infrequently, is of great importance because of its proclivities as a relentless killer. Those so afflicted are almost certain to die of cancer at an early age unless radical surgery is instituted early. It is a familial or inheritable disease transmitted by both sexes and attacking both sexes. It appears to behave as a mendelian dominant.

J. P. Lockhart-Mummery,[7] of St. Mark's Hospital, London, points out that an interesting feature of the disease from the standpoint of its being hereditary is that it differs from most hereditary diseases such as hemophilia, albinism,

deaf-mutism, *etc.*, in the respect that children are not born with it but tend to develop the condition about the time of puberty or during early adult life. In a few cases it may not develop until early middle age. On this score it is similar to hereditary amaurotic family idiocy, or hereditary optic atrophy.

In his classical discourse on the origin of cancer, Lockhart-Mummery has gone on to contend that in the light of our recent knowledge of biology a veil has been lifted and that the way may soon be clear to an establishment of the fact that many diseases of hitherto unknown origin may be shown to have as an underlying or antecedent factor this same kind of genetic background.

The crux of the whole matter is held to depend upon the tendency towards a genetic mutation of somatic cells. Just where the mutation started is difficult in most instances to say. In the case of hemophilia, it seems fairly certain that it began in some ancestor of the Coburg royal family several hundred years ago. In adenomatosis, as in other diseases of genetic origin, the results of a mutation of the genes may appear in succeeding generations either as dominants or recessives; if as a mendelian dominant, the disease will tend to occur in every generation. This is true of adenomatosis. If the condition is a recessive it will be necessary for both parents to carry the mutative genes. This may not occur for a great many generations and the hereditary factor will consequently in all probability not be recognized.

It appears reasonably clear in adenomatosis that the hereditary factor consists of the tendency of the epithelial cells of the large bowel to proliferate. This occurs in the majority of cases at an early age and results in the development of countless simple adenomata, any and all of which carry the potentialities of developing, with time, into an adenocarcinoma by reason of further imposed mutation of its component cells.

This explanation may seem fantastic to some, and to fall into a category belonging to the realm of logomachy. In any event, the two important facts which seem to have been conclusively proven and which must be accepted are that: first, adenomatosis or multiple polypoid disease of the colon is an inheritable condition; and, second, that malignant supervention is inevitable at an early age in practically 100 per cent of such cases. The first of these truths constitutes a distinct indication for investigating other members of a family, one member of which is found to be so afflicted. The second constitutes a justification for the institution of such a formidable operative procedure as total colectomy which was done in one of the cases here reported (Figs. 3 and 4).

When the polypi in the rectum and rectosigmoid are not too numerous to permit their removal by fulguration through a sigmoidoscope, certainly the operation of choice is to perform a side-to-side ileosigmoidostomy, as a first stage, and several weeks later a resection of the short-circuited large bowel as the second stage of a two-stage operation. This was done in the second case of our series (Figs. 8 and 10).

While proctosigmoidoscopic examination will reveal the presence of

polypi in the majority of instances, no patient should be considered conclusively examined until a roentgenologic study of the colon has been made. The importance of a contrast film following the injection of air after the barium has been evacuated cannot be overemphasized. This fact is strikingly revealed by the roentgenograms shown in connection with this report (Figs. 1, 2, and 7a, b and c).

CASE REPORTS

Case 1.—K. C. W., age 28, a Water Tender First Class, was admitted to the proctologic service of the U. S. Naval Hospital, San Diego, Calif., March 1, 1943, with an established diagnosis of hemorrhoids.

FIG. 1.—Case 1 (K.C.W.): Roentgenogram of large bowel showing partial evacuation of enema. Adenomatosis indifferently shown.

The patient had noticed occasional bleeding from the rectum, and the occasional protrusion of a soft mass from the anal outlet for a period of ten months. During the past two years he had passed four to six soft to watery stools daily.

On digital examination of the rectum there was noted a soft, polypoid mass on the anterior wall of the lower third of the rectum. Proctosigmoidoscopy to a distance of 24 cm. revealed numerous polypi and polypoid masses, small to medium size, as far as examined. No normal looking mucosa was seen. Specimens of tissue were obtained for microscopic study. General physical examination showed nothing abnormal.

Roentgenologic studies of the upper gastro-intestinal tract were negative. The roentgenologist's report of his study of the colon is quoted in full:

"Roentgenologic examination of the large bowel by barium enema shows no delay to the passage of barium. However, there are numerous smooth, intrinsic filling defects visible throughout the colon from the rectum to the cecum. These measure about 0.5 to 1 cm. in diameter and appear to be in proximity to one another, so that almost the entire mucosa is involved. There is very little normal intervening mucous membrane.

FIG. 2.—Case 1 (K.C.W.): Following inflation of colon with air, extensive polypoid disease is revealed.

"Films taken after the evacuation of barium and following the introduction of air into the bowel show the above described polypi to involve the entire mucosa of the colon (Figs. 1 and 2).

"Impression: Polyposis of the entire colon."

The diagnosis was changed from hemorrhoids to polypi, multiple, colon.

The Tumor Board, upon reviewing this patient's problem, concurred in our recommendation that a complete colectomy be performed.

On May 10, 1943, a single-barrel ileostomy was established under spinal anesthesia supplemented by intravenous anesthesia (sodium pentothal). Convalescence was rapid and uneventful (Fig. 5).

On July 17, 1943, the second stage was undertaken. The large bowel was removed, including ileal stump, cecum, ascending, transverse, descending, and sigmoid portions of the colon as far as the rectosigmoid. The rectosigmoid was left buried beneath the reconstructed pelvic floor. A drain left in the hollow of the sacrum was brought out through a stab wound near the tip of the coccyx. Ten grams of sulfanilamide were placed in the coelomic cavity. Anesthesia comprised continuous spinal and intravenous sodium pentothal.

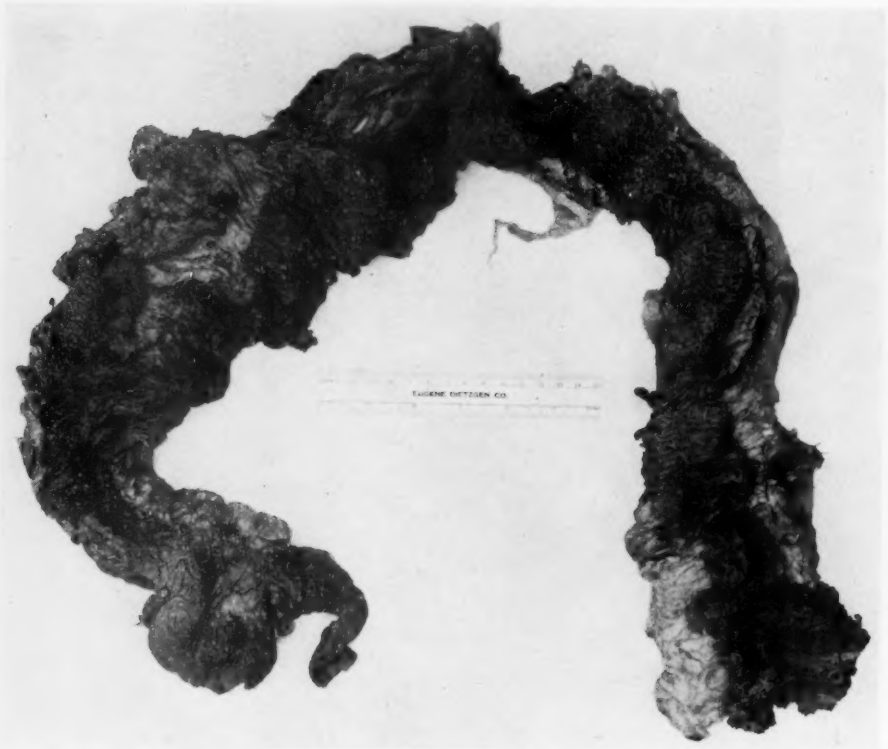

FIG. 3.—Large bowel, Case 1 (K.C.W.): Mucosa was studded with myriads of polypi, however, photographic scale is too small to show individual lesions.

Convalescence from this extensive procedure was uneventful until July 31, 1943, when the patient developed severe abdominal cramps and pain. The ileostomy suddenly ceased functioning. Attempts to pass a Miller-Abbott tube beyond the stomach were unsuccessful. Roentgenologic examination of the abdomen was suggestive of intestinal obstruction.

On August 1, 1943, an exploratory celiotomy was done and a loop of ileum was found adherent to the parietal peritoneum in the right upper quadrant and obstructed. A small abscess was discovered at the site of obstruction. The adherent bowel was freed, a cigarette drain was placed through a stab wound, and sulfanilamide crystals were placed in the abdominal cavity. Convalescence from this emergency procedure was uneventful.

On September 2, 1943, several small sessile polypi in and about the ileostomy stoma were destroyed by means of fulguration. The terminal ileum was examined to a distance of 14 cm. by means of the small caliber proctosigmoidoscope. No other polypi were noted.

On October 7, 1943, the final stage was undertaken—a perineal excision of the rectosigmoid, rectum, and anal canal (Fig. 4). Technically, this was indeed difficult because of the unusually long period of time between the second and third stages, occasioned by the surgical treatment of the acute intestinal obstruction.

All specimens were examined carefully. The pathologist reported no evidence of malignancy.

FIG. 4.—Pen drawing of rectum, Case 1 (K.C.W.): Showing multiple polypoidosis.

The patient's convalescence was satisfactory following the perineal excision. The perineal wound healed completely and bladder function was normal. He was ultimately discharged to limited duty wearing an ileostomy bag. There was no skin irritation around this ileostomy (Fig. 5) and the intestinal excreta had become semisolid in

consistency. The manner in which this patient became reconciled to his ileostomy and adapted himself to the use of an ileostomy bag was indeed gratifying.

This patient presents an interesting and suggestive family history (Fig. 6). We should like an opportunity to examine the three sisters who are said to be living and well; such examination has been advised.

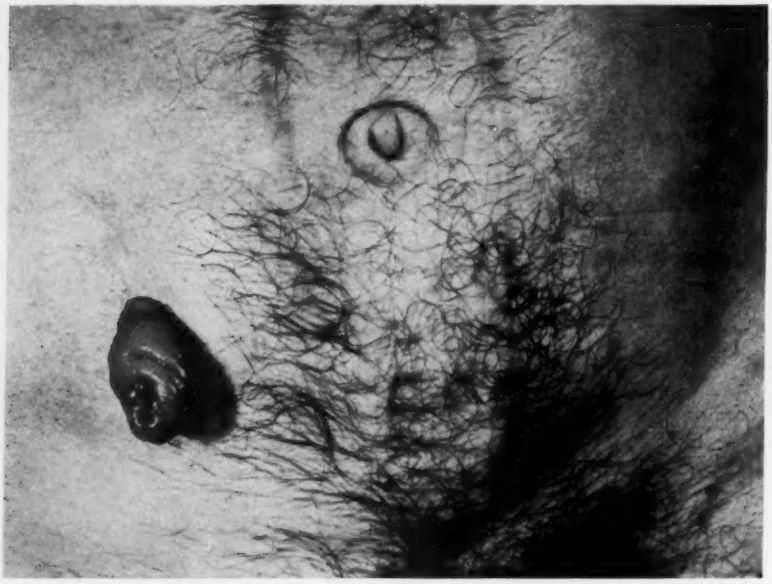

FIG. 5.—Case 1 (K.C.W.): Single-barrel ileostomy.

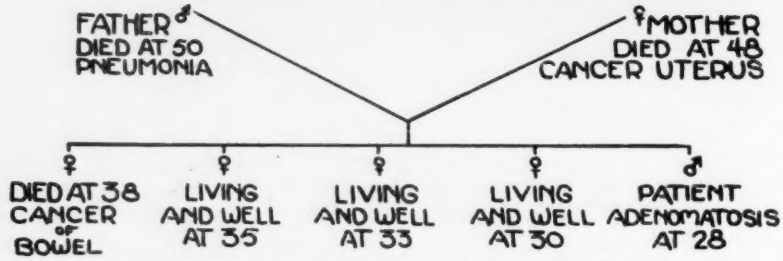

FIG. 6.—Diagram of family history of Case 1 (K.C.W.).

Inasmuch as the patient is married the question arises as to the advisability of his having children, in view of the mendelian possibility of his offspring developing polypoid disease of the large bowel.

We believe that this patient is permanently cured and that several factors have contributed to the successful outcome. (1) It was fortunate that the patient's polypoid disease was discovered before demonstrable malignant changes had developed. (2) The patient's attitude and willingness to cooperate were marvelous. When this man was confronted with the facts concerning his disease and the serious nature of it and the very definite risk the radical surgical treatment entailed, he promptly made up his mind that he was ready for treatment and that he was going to get well. One could not

FIG. 7a

FIG. 7b

FIG. 7c

FIG. 7a.—Roentgenogram, Case 2 (J.G.): Showing large bowel filled with barium. Only a suggestion of polypi is discernible.

FIG. 7b.—Case 2 (J.G.): Following partial evacuation of barium, polypi become evident in several segments of large bowel.

FIG. 7c.—Case 2 (J.G.): Following inflation of bowel with air, presence of multiple polypoidosis is strikingly demonstrated.

ask for a patient in better physical condition and in a better frame of mind. (3) In all four stages of the surgical management, the teamwork of surgeon and anesthetist was most satisfactory.

FIG. 8

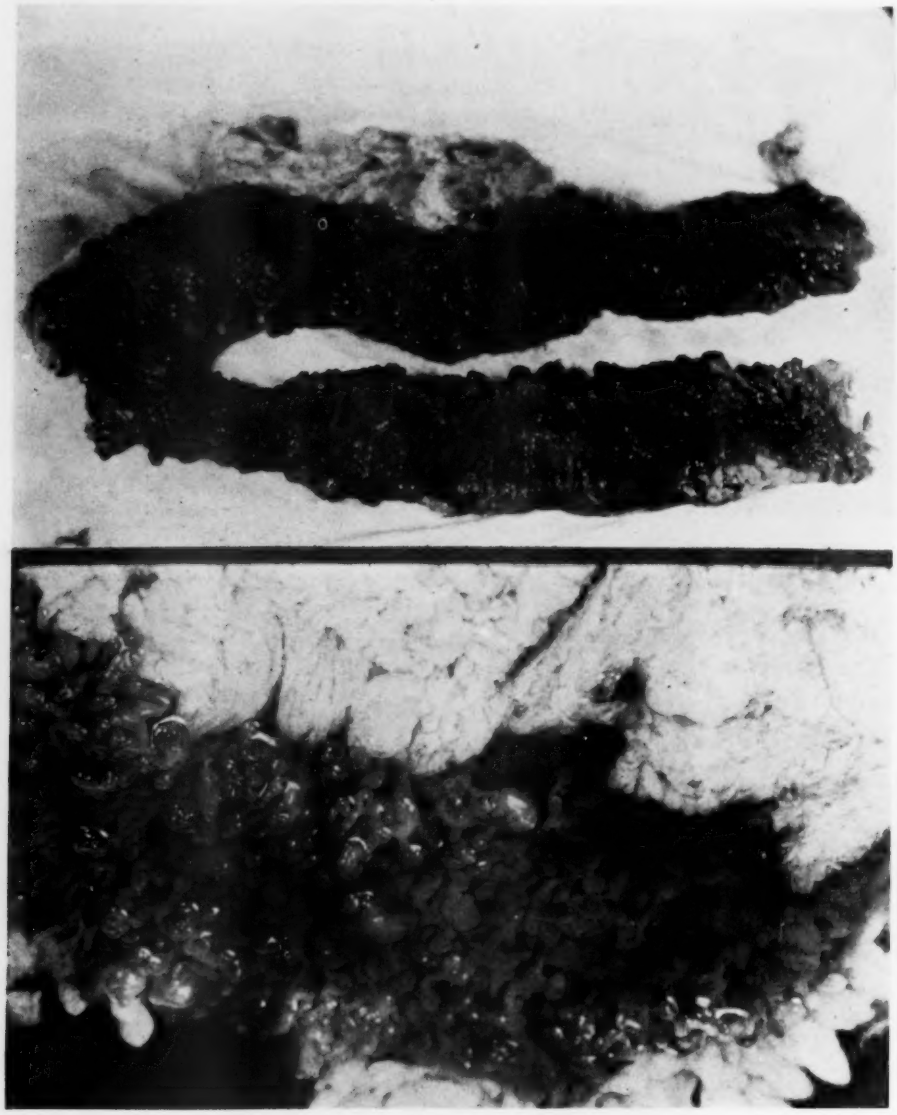

FIG. 9

FIG. 8.—Large bowel, Case 2 (J.G.): Showing multiple adenomata.
FIG. 9.—Segment of transverse colon, Case 2 (J.G.); taken under water: Showing countless adenomata.

Case 2.—J. G., age 38, an Apprentice Seaman, was born in Tepeyjanez, Mexico. He entered the United States Navy, July 3, 1943, as a Mexican national. He was admitted to the sick list, December 27, 1943, with a "Diagnosis Undetermined (colitis, chronic)." His chief complaints were recurring abdominal pain, occasional vomiting,

and diarrhea at intervals (4–5 stools daily) for five years—stools sometimes contained blood. In 1939, he was examined roentgenologically twice; the second examination was thought to indicate the existence of a stomach ulcer. This, however, was never confirmed. Family history was suggestive of a carcinomatous predisposition. The mother,

FIG. 10.—Case 2 (J.G.): Roentgenogram showing functioning ileosigmoidostomy after large bowel had been removed.

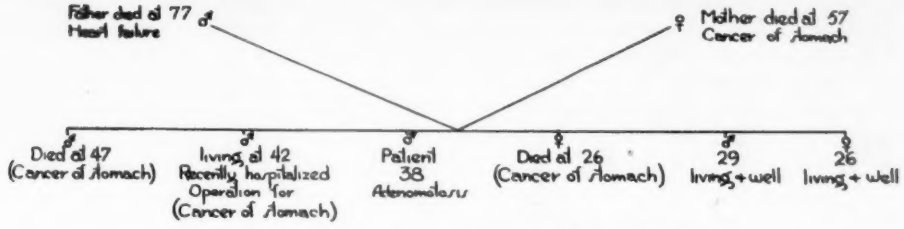

FIG. 11.—Case 2 (J.G.): Diagram of family history.

one brother and one sister were said to have died of cancer of the stomach. One brother, recently hospitalized, was said to have cancer of the stomach.

Physical examination upon admission revealed a swarthy Mexican of medium stature. Tenderness, with muscle guarding, was elicited in all abdominal quadrants.

Proctoscopic examination revealed internal hemorrhoids, Grade 2, and numerous small sessile polypi, with intervening mucosa of normal appearance. There was no evidence of an ulcerative colitis. Barium enema and roentgenologic study revealed a honeycomb irregularity of the barium contour of the colon throughout its entire extent, but the departure from normal was slightly more prominent in the left half of the large bowel. After evacuation of the barium, air injection of the colon strikingly demonstrated almost complete coverage of the mucosal lining with rounded granulomata or small polypi averaging 3 Mm. in diameter. These changes were minimal in the cecum and ascending colon, but from the hepatic flexure to the upper rectum there appeared to be more involved mucosa than uninvolved space between (Fig. 7a, b and c). It was interesting to note that in spite of this extensive involvement, there was an average tone to the large bowel, the diameter of which was average in size and normal haustration and mass movements were observed. Irritability and tubular configuration of this bowel, the characteristic signs of colitis, were constantly absent. Gastro-intestinal roentgenology revealed no evidence of cancer in the upper G. I. tract. The duodenal cap showed a deformity along its lesser curvature side. There was no ulcer crater demonstrable on the lesser curvature. Within four hours the stomach had emptied completely, demonstrating the absence of obstruction. The small bowel appeared to be normal. The findings suggested scarring of the cap as a result of an old healed duodenal ulcer. Oral cholecystograph showed a normally functioning gallbladder and no evidence of stones.

Through the sigmoidoscope all of the adenomatoma from the pectineal line to the pelvic sigmoid were fulgurated and following healing the bowel mucosa was free of evidence of polypoid disease.

On January 1, 1944, under spinal anesthesia and through a suprapubic incision, a side-to-side ileosigmoidostomy was established between the terminal ileum and the pelvic sigmoid (Fig. 10). The patient's convalescence following this operation was uneventful. The operative wound healed by first intention, and aside from a diarrhea amounting to from 5 to 10 stools daily which lasted about two weeks, the bowel function returned to normal and the bowel movements were reduced to an average of 2 to 3 daily. The patient was somewhat anemic and received several transfusions during the first three postoperative weeks.

The second part of his operative procedure was planned for the latter part of February; however, an acute tonsillitis with peritonsillar abscess supervened and after the acute process subsided, the patient was transferred to the Eye, Ear, Nose and Throat Service for a tonsillectomy. Tonsillectomy was done on March 29.

On April 20, 1944, under spinal anesthesia, through a long left rectus incision, the terminal ileum was divided. The distal end of the ileum was closed and a colectomy which included the entire large bowel from the cecum to the site of the sigmoidal anastomosis with the ileum was performed (Fig. 8). The proximal end of the sigmoid was closed. The peritoneum and rectus fascia were closed with interrupted stainless steel wire sutures. Healing of the operative wound was again by first intention, and save for a temporary threat of small bowel obstruction following this operation, the patient's convalescence was uneventful. Bowel function was not interrupted. He was allowed up and about on the tenth postoperative day and within a month the patient was entirely symptom free subjectively and he was having one or two formed stools daily.

Gross examination of the excised colon revealed an 80-cm. segment including a stump of ileum, the cecum and appendix with omentum attached to the midsegment of the bowel. The mucus surface was studded with multiple polypi varying in size from pinpoint to 1.5 cm. in diameter; some were attached to long pedicles (Figs. 8 and 9). At the splenic flexure of this bowel segment, in the mesentery attachment, there was a large area of induration 10 x 5 cm. This was separate from the bowel wall. The mucosa adjacent to this area was not different from the rest. Microscopic examination

revealed no evidence of malignant degeneration in any of the several polypi examined. The above referred to indurated mass showed no evidence of malignancy but consisted rather of fibrous tissue in which there was slight perivascular lymphocytic infiltration.

The patient's family history is diagrammatically illustrated in Figure 11.

CONCLUSIONS

1. Multiple polypoid disease of the colon is an inheritable condition attended by an extreme predisposition to malignant degeneration early in life.

2. The importance of the use of barium enemata and a contrast film following injection of air as a diagnostic measure is emphasized.

3. Radical surgical intervention, namely, total colectomy, is warranted, and carries with it the only hope of permanent cure.

4. Ileosigmoidostomy followed by resection of the intervening segment may be done in lieu of total colectomy in cases where the lesion in the rectum and rectosigmoid can be removed by fulguration.

5. Two case reports are added to the literature. The first is illustrative of one, the second of the other of the surgical procedures referred to.

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PORTAL VEIN THROMBOSIS FOLLOWING REMOVAL OF RUPTURED SPLEEN

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THROMBOSIS of the splenic and portal veins is a not uncommon, though often unrecognized complication following splenectomy.[1, 2, 3] This operation is occasionally followed by fever, sometimes chills and sweats, vague gastro-intestinal symptoms including abdominal pain, nausea, vomiting, and distention which are prolonged and not easily accounted for. It is suggested that in many of these cases some degree of pylethrombosis exists.

Ordinarily the gastro-intestinal symptoms persist for only a short time then clear and the patient recovers. It is possible that readjustments in the portal blood flow made necessary by removal of the spleen, partial thrombosis of the portal vein or its tributaries, or both, may account for the symptoms. The subsequent disappearance of symptoms may be explained on the basis of establishment of collateral circulation or recanalization of the thrombosed vessels.

The literature contains numerous references to the subject of portal vein thrombosis.[4, 5, 6] In the main, these are concerned with the medical aspects of the problem. The literature on thrombosis following splenectomy has been well summarized by Davis and Sharpe.[7] This complication seems most likely to occur in splenic anemia. In 1895 Delatour[8] reported a case which demonstrated this complication. Mayo[9] stated in this regard: "Of the ten per cent of patients who died in the hospital following splenectomy the majority died of progressive thrombophlebitis extending from the splenic pedicle into the portal vein."

The studies of Rosenthal,[10] and others,[11, 12] have indicated the importance of the platelet count in predicting the chances of thrombosis postoperatively in this disease. The thrombocytopenic group seemed to recover without incident, while those in the thrombocythemic group had a high incidence of portal thrombosis.

Davis and Sharpe[7] reported a case of splenic and portal vein thrombosis following splenectomy for hemolytic jaundice. So far as we are able to determine, this condition has not been reported as a postoperative complication in thrombocytopenic purpura.

Eliason and Stevens[13] report no deaths from portal thrombosis in a large series of cases subjected to splenectomy for splenic anemia, thrombocytopenic purpura, and ictero-anemia.

Thrombosis of the portal vein has also been reported following traumatic rupture of the spleen in which no operation was performed.[14] One gets the impression from various writers that splenic vein and portal vein thrombosis

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is a frequent complication of splenectomy in general. However, so far as we can ascertain no cases have been reported in which this complication followed the removal of a ruptured spleen. We believe the present case represents an instance of portal thrombosis subsequent to removal of a ruptured spleen which, in turn, precipitated an acute cholecystitis on the basis of a previously diseased gallbladder. It seems likely that interference with venous drainage was sufficient to cause edema and infarction of the gallbladder wall, and this together with stones led to obstruction of the cystic duct. This conception of the pathogenesis is in agreement with the teachings of the late Edmund Andrews.[15] Death resulted from shock and hemorrhage following cholecystectomy.

Simonds[6] in a comprehensive review of the subject of portal thrombosis, stated: "alterations in composition of the blood, slowing of the blood flow, and injury to the lining of the vessel have been accepted as the fundamental factors of causation of thrombosis in general since the pioneer but thorough work of Cohnheim and Welch."

The factors predisposing to thrombosis, cited by Simonds, which seem to be of importance in the present instance are:

(1) Alteration in the composition of the blood. The presence of a marked platelet increase following splenectomy ranging up to about 1,500,000 on the eighth day is demonstrated in the report of Rousselot and Illyne.[16] Thrombocytosis and leukocytosis are said to persist.[17] Other factors to be considered are: operative shock, dehydration, and alterations in serum proteins.

(2) Alteration in portal blood flow occurs by virtue of the ligation of the splenic vein. It is estimated that normally about 20 per cent of the portal blood volume is carried by the splenic vein (Burton-Opitz, Mayo). Removal of this supply results in decreased portal flow. One would anticipate thrombosis of the distal portion of the splenic vein. Should the process progress it seems clear that the portal vein may be involved by thrombosis or embolism stemming from the splenic vein.

(3) Alteration in the wall of the splenic vein secondary to operative trauma. This factor may vary according to the technical difficulties involved. There is no doubt that tissue trauma is greater when the spleen is large, adherent, or otherwise difficult to remove. It is to be expected that splenectomy under emergncy conditions may be somewhat more traumatic than in the elective operation.

(4) Inflammatory changes in the splenic pedicle or adjacent structures resulting from the initial trauma to the abdomen or from absorption of the tissue of the splenic pedicle, blood clots, *etc.* In some instances local sepsis may contribute to thrombosis of the splenic vein or portal vein.

(5) Previous diseases of the portal vein such as phlebosclerosis and syphilis may provide sufficient basis for thrombosis when other factors are superimposed.

Case Report.—A. R., white, male, age 35, a shipyard worker, entered Providence Hospital February 21, 1943. Five hours before admission the patient had fallen across an iron rail striking his left lateral costal margin. He stated that moderately severe pain occurred immediately and he felt "knocked out." Later the pain became generalized, but was especially marked in the left upper quadrant. There was pain on movement or deep inspiration, but no pain referred to the left shoulder. There was no nausea or vomiting.

The past history revealed that the patient had been perfectly well except for an attack of acute abdominal pain which had been diagnosed gallbladder trouble in 1937.

Physical Examination.—Temperature, 98° F.; blood pressure, 106/60; pulse, 100. The patient was pale and perspiring profusely. Considerable pain was noted on inspiration. Over the left 10th rib in the midaxillary line there was an area of ecchymosis 2.5 cm. in diameter. There was no evidence of fracture of the rib. The lung fields were clear. The heart was not enlarged. The tones were somewhat distant, but there were no murmurs. The abdomen was slightly distended and tympanitic to percussion. There was some bulging of the flanks, but neither shifting dullness nor fluid wave could be demonstrated. The extremities were normal. The remainder of the physical examination revealed no changes.

Laboratory Data.—Hemoglobin, 93 per cent (12.83 Gm.), R. B. C., 4,290,000; W. B. C., 14,600. Differential count: P.M.N. 64, staff cells 18, small lymph, 11, monocytes 7; sedimentation rate: 1 Mm. in 15 min., 8 Mm. in 45 min. Urine showed albumin 2 plus, pus cells 2 plus, red cells negative and bacteria 1 plus. The Kahn test was negative.

Examination of the blood three hours after admission revealed that the hemoglobin and red cell count were essentially the same, but that the white blood cell count had risen to 16,500, and the P. M. N.'s were reported as 72 and the staff cells 16.

It was our impression that the patient had a ruptured viscus, almost certainly the spleen. The patient was observed for a period of three hours during which time the signs and symptoms did not change appreciably. He continued to have diffuse abdominal pain and tenderness, direct as well as rebound, especially in the lower abdomen. The spleen was not palpable. The pulse rate remained elevated. The blood pressure showed no tendency to fall. Because of failure to improve and the very suggestive picture of intraperitoneal hemorrhage secondary to rupture of the spleen, operation was advised and performed.

Operation.—Under closed cyclopropane, oxygen and ether anesthesia, a long left upper rectus incision was made. Many large blood clots together with a large quantity of free blood was encountered, chiefly in the region of the spleen. The spleen was moderately enlarged and two deep lacerations were present over its convex surface. There was active bleeding from this area. The liver appeared normal. The gallbladder was not examined.

The spleen was delivered and its pedicle was doubly clamped and cut. The pedicle was tied with No. 2 chromic catgut transfixion sutures. When complete, the operative field appeared dry and the blood clots were removed. The wound was closed.

The patient received 1000 cc. of 5 per cent glucose in normal saline in the operating room, and 400 cc. of plasma following the operation. His blood pressure dropped to 84/56 toward the end of the procedure and remained at about this level during the night. The following morning the hemoglobin was 75 per cent (10.35 Gm.), and the red cell count 3,540,000. The postoperative course was characterized by frequent nausea with occasional emesis. A considerable degree of paralytic ileus with distention was observed from the second to the fifth postoperative day. The patient had a disturbing cough and expectorated a moderate quantity of thick mucus from time to time, but there was no demonstrable atelectasis or pneumonia. The temperature rose to 101.4° F. on the day following operation, and slight daily elevations averaging about one to two degrees above normal were observed until discharge from the hospital on the seventeenth postoperative day.

On the night prior to expected discharge from the hospital the patient complained of steady severe pain in the left upper quadrant together with profuse sweating and weakness. This episode seemed to follow the ingestion of food. The pain was not relieved by changes in position, but gradually disappeared after administration of morphine. The following day the patient felt well and was discharged from the hospital, March 13, 1943, apparently recovered.

While at home the patient had recurring attacks of pain localized to the left upper abdomen. The pains were never cramping in type nor was it associated with nausea or

vomiting. They seemed to occur immediately after eating. There was no disturbance in bowel function, and no significant rise in temperature at this time. There was no abdominal tenderness or distention. Because of persistence of pain the patient was readmitted on March 16, 1943.

Blood Examination.—Hemoglobin, 86 per cent (11.87 Gm.); R. B. C., 4,610,000; W. B. C., 13,350; P. M. N., 54; S. L., 40; staff cells, 6. Sedimentation rate: 20 in 15 min., 66 in 45 min.

Roentgenograms of the chest showed slight elevation of the right leaf of the diaphragm, but the lung fields appeared normal, and one of the abdomen showed the entire colon to be filled with gas, but no evidence of small bowel distention.

It was our impression that the patient had a residual collection of pus or blood in the left upper quadrant and conservative treatment was outlined.

The following day the pain had shifted to the right upper quadrant and there was definite tenderness and muscle spasm over the region of the gallbladder. There was no nausea or vomiting. The temperature rose to 101.4° F., and the pulse rose to 128 per minute during the day. The patient continued to complain of pain over the gallbladder area, and careful investigation of his past history revealed that a similar episode had occurred in 1937, at which time the diagnosis of gallbladder disease had been made. On March 22 slight jaundice was present. The icterus index was 22. Under conservative measures the patient gradually improved. The pain and tenderness subsided and the jaundice disappeared.

On March 29, the blood examination showed: W. B. C., 8,600; P. M. N., 63; P. M. E., 3; S. L., 22; mono., 6; staff, 6. Sedimentation rate: 32 in 15 min., 100 in 45 min. The icterus index was 10.

The patient's general condition appeared good. He was prepared for operation by the administration of a high carbohydrate, high protein, and low fat diet as well as vitamin K and bile salts. On March 31, 12 days after onset of acute right upper quadrant pain, operation was undertaken for subsiding acute cholecystitis, with probable cholelithiasis and choledocholithiasis. The patient appeared to be a satisfactory surgical risk, however, it was later learned that he had repeatedly stated to others that he would not survive operation.

Operation.—March 31, 1943.—Anesthesia: cyclopropane, oxygen and ether. When the abdomen was opened through a right upper rectus incision, the gallbladder was found to be entirely walled-off by dense adhesions between omentum and the duodenum. The adhesions were extremely vascular and bled freely on slight trauma. The gallbladder was tense, dilated, and friable. It appeared markedly inflamed and contained a number of gallstones. The structures about the porta hepatis were, likewise, edematous and friable. The cystic duct contained impacted stones. The common bile duct felt normal to palpation. Because of subsequent events, adequate exploration of the common duct was not carried out.

Following freeing of adhesions between the gallbladder and the surrounding structures and the exposure of the common duct, profuse hemorrhage was encountered. This appeared to be venous in type. Attempts to control the bleeding by compression of the structures of the porta hepatis and ligation and application of hot wet packs were unsuccessful. The tissues were so friable that clamps or ligatures would not hold and each manipulation resulted in increased bleeding. It seemed that the hemorrhage came from one of the tributaries of the portal vein. During the period when packing was in place the gallbladder was removed from the fundus down to the cystic duct. The cystic vessels and the cystic duct were separately cut, clamped and ligated. The patient received plasma transfusion during the procedure and was also given caffein. Upon completion of the procedure his condition was poor and a gauze pack was left in the bleeding area and brought out the upper end of the wound.

The patient failed progressively, in spite of blood and plasma transfusions, and

expired four hours later. The clinical cause of death appeared to be operative hemorrhage and shock.

Pathologic Examination.—Surgical Specimens (Dr. T. D. Robertson): *Spleen* (Fig. 1): The spleen weighs 340 Gm. Two tears are present on the diaphragmatic surface of the spleen. The first measures 11 cm. in length, and the second is a V-shaped tear measuring 7 cm. A third tear is present on the left margin and measures 5 cm. *Pathologic Diagnosis:* Multiple traumatic rupture of the spleen, with hemorrhage.

FIG. 1.—Drawing of spleen showing lacerations containing some clotted blood.

Gallbladder: The gallbladder is a rigid, thick-walled structure 9 cm. in length and 3 cm. in diameter. The serosal surface is hemorrhagic and covered with a fibrin coating. The wall shows hemorrhagic mottling, fibrosis, and reaches a maximum thickness of 1.0 cm. There is bile-staining of the mucosa and yellow cholesterol streaking. It contains several cholesterol stones. Microscopic examination shows the wall to be thick and the site of extensive hemorrhage. There is some coagulation of the mucosal surface associated with the diffuse hemorrhage. There is infiltration by pus cells, eosinophils, and lymphocytes. Near one area of deep ulceration a number of foreign

body giant cells are seen. *Pathologic Diagnosis:* Marked hemorrhagic acute exacerbation of a chronic cholecystitis, with cholelithiasis.

Postmortem Examination (Dr. T. D. Robertson): The only significant changes are found in the abdomen. Approximately 300 cc. of bloody fluid is present in the right upper abdomen. Careful search for the bleeding point failed to reveal it. The tissues in the region of the common duct are indurated. The common duct is dilated and near the ampulla there are eight small mulberry cholesterol stones none more than 4 Mm. in diameter. The hepatic artery is then followed throughout and shows no bleeding point. The ligatures on the cystic artery and duct are intact. The portal vein (Fig. 2) is found after dissecting through edematous fibrous tissue, and it is noted

FIG. 2.—Drawing of liver, pancreas, duodenum, accessory spleen and portal vein and its tributaries. Note extent of thrombosis. The gallbladder had been removed at operation.

that it is filled with an adherent, rather mushy, red blood clot which is definitely a thrombus. It extends into the right and left branches as a firm, adherent, pink clot. The right lobe of the liver is much softer than the left, indicating probably more blood was cut off in the right lobe than in the left. This clot extends in a polypoid manner for a distance of 6 cm. into the upper portion of the superior mesenteric vein. The splenic vein is small, contracted, 8 Mm. in diameter, and filled by red to brown clot. The splenic artery is found at its distal portion to be tortuous and filled by dark red clots for a distance of about 2 cm. There is an accessory spleen measuring 3 cm. in diameter. The pancreas is somewhat edematous. The liver is enlarged and appears fatty. The right lobe is friable and shows diffuse red stippling. The splenic bed is

filled by adhesions. There are no blood clots found. The small intestine and colon appeared unchanged. The adrenal glands and other abdominal organs show no changes.

Microscopic Examination.—Pancreas: Except for postmortem autolysis the pancreas is not unusual. *Liver:* The central lobular hepatic cells are undergoing disintegration with pyknosis of nuclei and fragmentation. A slight increase in pus cells in some areas is noted. The sinusoids contain very little blood. Central lobular hepatic cells also contain large and small fat droplets. *Small Intestine:* There is no edema or other change. *Lung:* There is slight engorgement of the vessels. *Kidney, adrenal glands, myocardium:* No changes.

Pathologic Diagnosis: Death due to postoperative shock following cholecystectomy. Probably contributing much to this was liver deficiency on the basis of portal vein thrombosis. This was built up from a thrombus of the splenic vein, which probably followed previous splenectomy for traumatic rupture of the spleen.

Histologic examination of various levels of the portal system; the representative areas from which photomicrographs were made, are indicated in Figure 3.

The splenic vein (Fig. 4) is occluded by a fresh thrombus, which only in focal areas shows early softening and attachment to the vessel wall. This section apparently represents an area some distance from the point of ligation of the splenic vein.

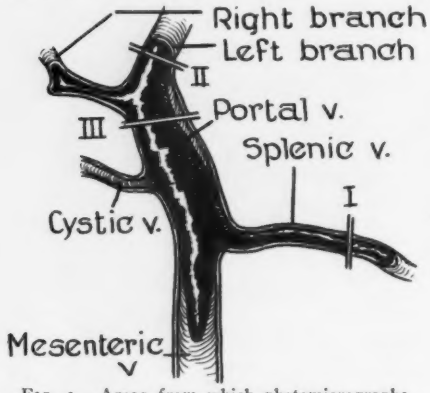

FIG. 3.—Areas from which photomicrographs were made.

The section through the left branch of the portal vein presents the picture of a truly organized thrombus. Here capillaries and fibroblastic proliferation constitute the predominant features of this also occlusive thrombus. Attachment to the wall of the vessel as well as beginning canalization has occurred (Fig. 5).

Section through the upper portion of the portal vein (Fig. 6) shows an occlusive thrombus of an age between the clot in the splenic vein and the organized thrombus in the left branch of the portal. A large area of central softening is noted as well as beginning organization of the circumferential attachment to the vessel wall.

Other sections taken from the more peripheral portion of the portal vein reveal fresher thrombus formation, apparently the result of propagation of the thrombus from above downward. Likewise, in that section taken through the right main branch of the portal system, a thrombus of earlier age than that in the left is noted.

COMMENT.—Following surgical ligation of the splenic vein the thrombus formed at this point must have been, in part, dislodged. This portion of thrombus, now circulating in the portal system, lodged in the left main branch of the portal vein producing an occlusion. The secondary attachment and the resultant organization of this thrombus then constituted a thrombus head from which retrograde propagation occurred. This propagating clot finally encroached upon the ostium of the cystic vein with obstruction to the venous return from the gallbladder. The resulting vascular stasis in this organ produced the clinical picture of acute cholecystitis.

DISCUSSION.—From the histologic studies in this case, it may be concluded that portal thrombosis occurred as a direct result of splenectomy. It must be borne in mind, however, that previous disease of the biliary tract may have

been a contributing factor. There is no evidence that direct or indirect trauma was of importance, since the blow received was relatively slight, well-localized and away from the upper abdomen.

The clinical course should have suggested this complication had not biliary tract disease been superimposed. Pallette[5] has pointed out that the symptoms resulting from portal thrombosis usually appear as sudden, acute upper abdominal pain which may appear in the right upper quadrant and simulate gallstone colic. In chronic thrombosis Simonds[6] notes that there may be no relationship to the taking of food. In the present instance eating usually precipitated the pain, which was at first located in the left upper abdomen. We believe, therefore, that the inadequacy of the portal system to

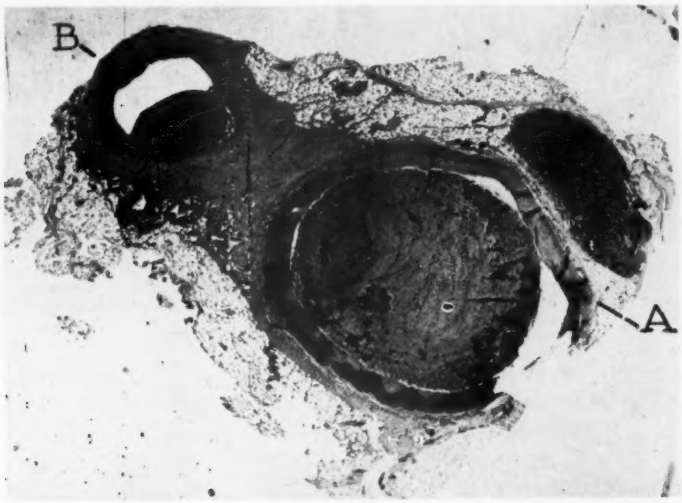

FIG. 4.—Fresh thrombus in splenic vein (A). Artery (B). (Low power). Note prominence of coral-like lamellae of congealed platelets, absence of organization indicating freshness of the thrombus.

meet the increased circulatory demands of digestion was sufficient to cause pain.

The presence of intermittent fever, leukocytosis, and increased sedimentation rate was evidence of serious intra-abdominal pathologic changes. In a case not complicated by biliary tract disease, it would seem that thrombophlebitis of the portal vein should be considered second only to an intraperitoneal abscess.

Intestinal dysfunction is dependent upon the degree of interference with the mesenteric veins. In this case there was little or no obstruction, but in Delatour's[8] classical case the symptoms were those of acute intestinal obstruction because of the cutting off of a large part of the circulation.

Bassler[18] has found that roentgenologic studies of the small intestine show marked slowing of the transit function from the jejunum down to the transverse colon in portal thrombosis. This again is dependent upon the degree of interference with the mesenteric venous flow, and it is unlikely that significant changes could have been demonstrated in this case. It is inter-

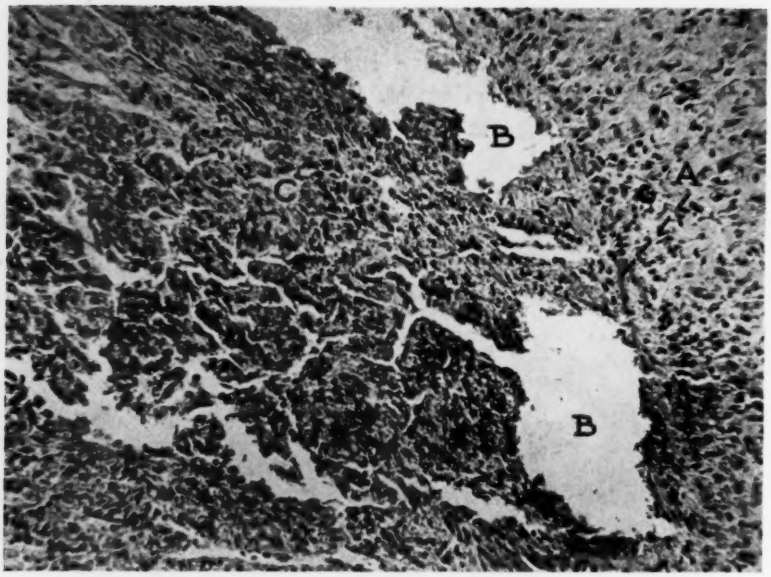

FIG. 5.—Organized thrombus in left branch of portal vein. (High power)
A. Intimal surface of vessel. B. Canalization. C. Organized thrombus.
Section showing organized occlusive thrombus and beginning canalization.

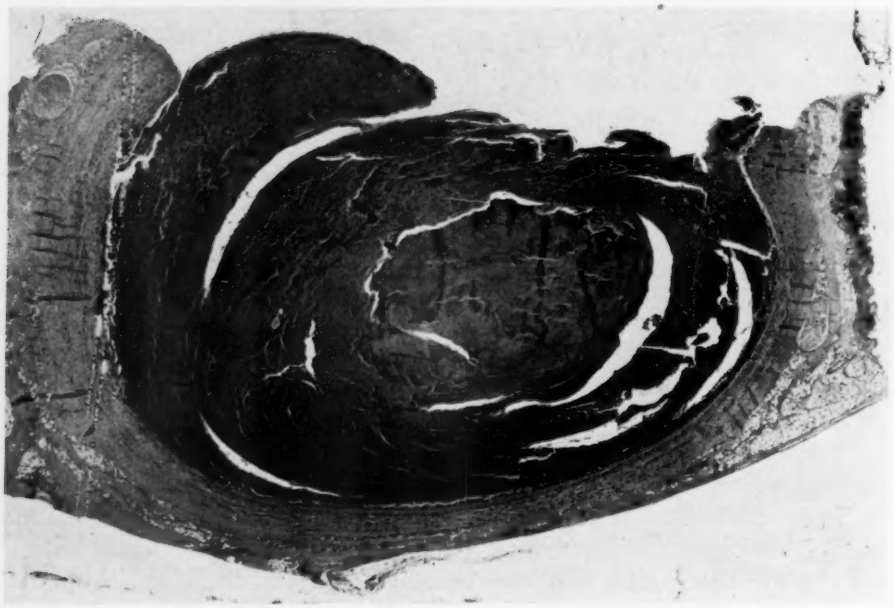

FIG. 6.—Organizing thrombus in upper portal vein. (Low power)
Note peripheral attachment with beginning organization of thrombus.

esting to note the degree of gaseous distention of the colon which was present in our case. It is suggested that portal blood flow may have been decreased sufficiently to cause diminished absorption of gas from the bowel.

Regarding the pathogenesis of an acute exacerbation of chronic cholecystitis in this patient, there seems to be no question about the rôle of vascular impairment. At operation, it was obvious that the venous pressure in the portal system greatly exceeded the normal. This back pressure through the cystic vein would seem to have been sufficient to lead to edema, infarction, hemorrhage and ulceration of the gallbladder wall.

At this time, it seems pertinent to remark that cholecystectomy should have been delayed for a much longer period. It is probably a good rule to delay all elective intraperitoneal operative procedures following splenectomy until adequate circulatory readjustments have been made. How long this might be is difficult to estimate. It is also to be recalled that reaction to shock and hemorrhage shortly following splenectomy may be decreased since the spleen is said to be an important organ of homeostasis.

Murray and MacKenzie[19] demonstrated clinically, and experimentally in dogs, that heparin can be of great value in preventing thrombosis of the portal vein following splenectomy and bowel resection for mesenteric thrombosis. This work suggests the possibilities of the anticoagulant drugs in the postoperative care of cases where this complication may be expected or suspected. This is particularly true for splenic anemia.

We were interested in the rôle the mental attitude of the patient played in the ultimate outcome. It has been repeatedly emphasized that patients who firmly believe they will not survive operation, frequently do not. Upon this basis most surgeons rightly will refuse to undertake operation. In this case, had we known of the patient's feelings in the matter it is likely that we too would have delayed. It is possible that had the patient not succumbed, recanalization and establishment of collateral circulation of sufficient degree to maintain good or fair health would have occurred.

CONCLUSIONS

1. A case of clinically unrecognized splenic and portal vein thrombosis following splenectomy for traumatically ruptured spleen is reported in detail.

2. In this case, acute cholecystitis on the basis of a previously diseased gallbladder is believed to have been precipitated by portal thrombosis which caused vascular changes in the gallbladder wall.

3. Death was caused by uncontrollable hemorrhage and shock during cholecystectomy. The increased portal venous pressure and friability of tissues made complete hemostasis unobtainable.

4. It is suggested that splenic and portal vein thrombosis following splenectomy may be a frequently unrecognized complication. Prolonged fever, abdominal pain sometimes related to food intake, abdominal distention, increased leukocyte count, and increased platelets and erythrocyte sedimentation rate following splenectomy should suggest to the surgeon the possibility of this complication.

5. Major elective abdominal operations should not be undertaken shortly following splenectomy if the possibility of portal thrombosis exists.

6. The anticoagulant drugs, heparin and dicoumarin, may be of value in preventing the onset or extension of thrombosis of the portal vein.

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ROENTGENOLOGIC EXAMINATION OF THE ABDOMEN AS AN AID IN THE EARLY DIAGNOSIS OF SPLENIC INJURY

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DAMAGE TO THE SPLEEN is probably the most common serious intra-abdominal injury resulting from blunt force. Clinically three types of bleeding may occur: (1) Extensive rupture with immediate massive hemorrhage, (2) small lacerations which ooze blood slowly over a period of hours or possibly days, and (3) delayed splenic rupture. These types of splenic damage have been discussed by many authors. By delayed splenic rupture is meant severe secondary hemorrhage occurring from the spleen days, weeks, or even months following the original injury. This type of bleeding occurs in about 14 per cent of all splenic injuries.[10]

In the first type of injury to the spleen the diagnosis is usually easily made and splenectomy carried out. The second and third types of splenic injuries are difficult to diagnose in the hours immediately following trauma, especially in the presence of associated injuries. The patient's symptoms and signs may disappear completely or so improve that he may be allowed to resume full activity. Then after a latent period of hours, days, or even months, secondary hemorrhage may occur, usually of such severity that circulatory failure ensues rapidly.

The time to remove a slowly bleeding spleen is early, before blood loss threatens life, and the ideal method of handling a delayed rupture of the spleen is to perform splenectomy early in the latent period. Diagnosis must, therefore, come early, and yet the difficulties of such early diagnosis are great. Clinical symptoms and signs may be equivocal, and the accessory examinations which the clinician has heretofore used may be dangerous, time-consuming, inconclusive, or all three.

Hematologic work may or may not aid. Abdominal aspiration or peritoneoscopy have been advocated, but these examinations are more difficult and more dangerous than the taking of a plain film of the abdomen. There is evidence that the roentgenologic examination of the abdomen can be of great aid in establishing early the diagnosis of a lacerated spleen.

Various authors have described roentgenographic aids in the diagnosis of lacerated spleen. Webb[9] reported increased density in the left upper abdominal quadrant, with elevation of the left side of the diaphragm, displacement of the stomach to the right, and free fluid between loops of intestine. Zabinski and Harkins[10] mention elevation of the diaphragm in one patient and medial displacement of the colon in another. They also mention Bancroft's experience in administering barium sulfate to a boy, placing him in the Trendelenburg position, and observing a mass in the region of the spleen displacing the

stomach. J. M. Deaver[3] mentions elevation and tenting of the left diaphragm in a patient with a delayed splenic rupture coming on 23 days after injury. Burke and Madigan[2] gave thorium dioxide to a patient with lacerations of spleen and liver and were able to outline the damage in each viscus. These roentgenologic procedures are helpful to a limited degree only. They are all either signs of advanced hemorrhage, as when visceral displacement is shown, or they are time-consuming, as is thorium, or they are undesirable for other reasons, such as the administration of barium orally.

The roentgenographic findings described by Solis-Cohen and Levine[5, 7] may answer the need for a reliable, simple means which will aid in the early diagnosis of minimal to moderately severe splenic damage. These authors, in making roentgenologic examinations of the abdomen in three patients suspected of having splenic injury, described obliteration of the splenic shadow, and a dilated stomach, with serration of the greater curvature. In each case the diagnosis was confirmed at celiotomy. In plain films of the abdomen taken of 100 patients with no demonstrable splenomegaly, the authors did not encounter these findings.

Various questions arise concerning these roentgenographic signs: (1) Does splenic laceration always cause them? (2) Are the signs dependent upon the size of the splenic laceration or the amount of hemorrhage? (3) Do they occur in damage to viscera other than spleen? (4) Are they present when the spleen plus some other viscus is damaged? (5) Why do these signs occur? (6) Are they present after splenectomy?

During the past few months on the Surgical and Urologic Services of the North Carolina Baptist Hospital and Forsyth County Hospital, three patients with nonpenetrating trauma to the left upper quadrant, left flank and left lower thorax have been studied.* A survey of the records of these patients tends to corroborate the findings of Solis-Cohen and Levine,[7] and lends evidence to help answer the above queries.

CASE REPORTS

Case 1.—N.C.B. No. 25507 (From the Service of Dr. H. H. Bradshaw): M. N., white, female, age 13, was admitted at 3:30 P.M., February 14, 1944, with a history that at 3:00 P.M. she had been struck and knocked down by a school bus. She was unconscious for 15 minutes, and when seen in the Emergency Room she had amnesia covering the previous 24 hours, although her memory for prior events was good. She complained of pain over the left lower chest and in the left upper abdominal quadrant. Blood pressure 124/72; pulse 100 to 110. Her occipital scalp was lacerated. The chest was clear and there was moderately severe left upper abdominal tenderness. There was suggestive increase in the area of splenic dullness. No flank rigidity was found, and peristalsis was quiet.

Accessory clinical findings were not remarkable save for a leukocyte count of 14,900, with a normal differential. Urinalysis revealed 40 to 50 white blood cells and 10 to 20 epithelial cells (h.p.f.), with one plus albumin, and a negative benzidine test.

A plain film of the lower chest and abdomen revealed fractures of the left seventh and eighth ribs posteriorly, without displacement. The kidney and psoas outlines were

* These patients were operated upon by members of the Resident Staff in Surgery, Doctors Felda Hightower, M. C. Bowman, and W. L. Molineux.

normal. The splenic shadow was not visualized, the stomach was displaced downward, and there was an unusual amount of gas in the stomach, with serrations of the greater curvature in the cardiac and midportions (Fig. 1).

She was observed several hours, with no change in the symptoms or signs. Celiotomy was performed at 8:20 P.M., February 14, 1944, under cyclopropane, oxygen, and ether anesthesia, using a curved left subcostal incision. Ecchymosis was present in all visible parts of the omentum, and 400 cc. of dark, liquid blood was found in the peritoneal cavity. On the concave surface of the spleen there was an irregular laceration six centimeters

FIG. 1.—Preoperative plain film of abdomen of Case 1, showing the left diaphragm and stomach outlined with India ink. Note downward displacement of gas-filled stomach and serrated greater curvature.

long, showing at its upper part, excavation into the splenic pulp. Postoperatively, the patient received 500 cc. of pooled plasma and 500 cc. of citrated blood. Her course was uneventful, she was discharged on the tenth postoperative day, and she has remained well since.

Films of her abdomen made postoperatively showed kidneys and stomach normal in outline, and position (Fig. 2).

Case 2.—F.C.H. No. 2847 (From the Service of H. H. Bradshaw): O. S. N., white, male, age 34, was admitted at 12:15 P.M. April 24, 1944, with a history that two hours earlier he had fallen from a barn, a distance of eight feet, and landed on his left side, striking his left flank. Following this he vomited once and had pain in his

left upper quadrant radiating down to his left lower quadrant and genitalia. The pain in his left upper quadrant increased and he noted pain in his left flank.

At the time of admission his temperature was 100° F.; pulse 88; blood pressure 130/78. Chest examination was negative. There was muscular rigidity of the left upper and left lower abdominal wall, with tenderness in the left upper abdominal quadrant. In the left flank and over the left lower ribs, there was a diffuse erythematous area, quite tender on even light palpation.

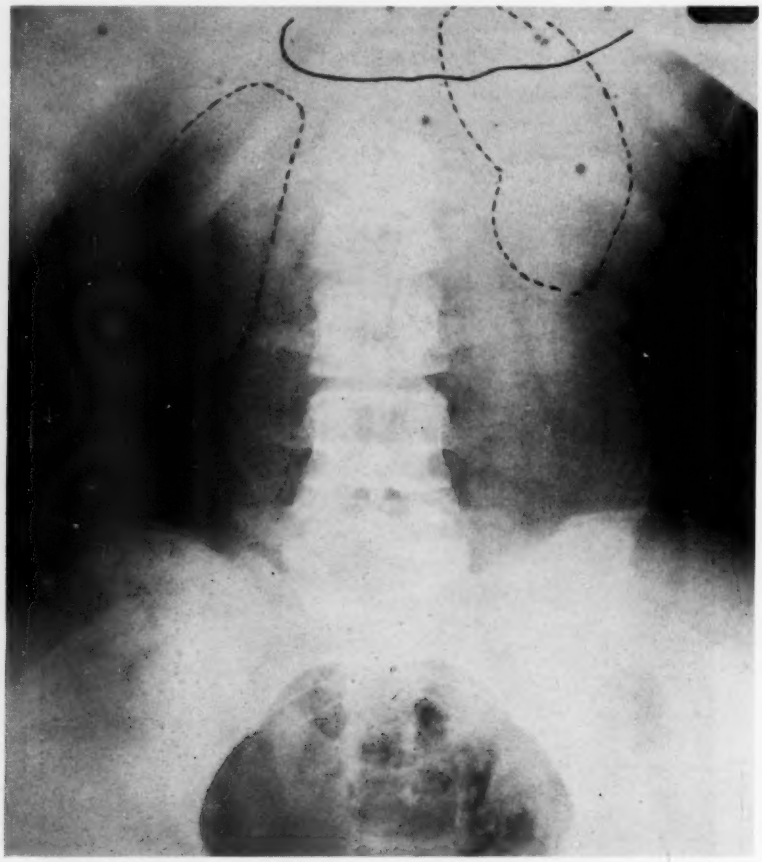

FIG. 2.—Postoperative film of abdomen of Case 1, showing the greater curvature of stomach and kidney shadows outlined with India ink. Film does not include diaphragm. Stomach is normal in position and greater curvature is smooth.

Accessory clinical findings showed four to six red blood cells and an occasional white cell (h.p.f.) in a voided urine specimen. Otherwise the findings were normal. A plain film of the abdomen showed moderate enlargement of the splenic shadow. The stomach contained much gas, the fundus was displaced downward, and the greater curvature was serrated (Fig. 3). The left kidney and psoas shadows were indistinct.

Celiotomy was performed three hours after admission, under cyclopropane, ether, and oxygen anesthesia. There was a small amount of ecchymosis in the mesentery of the splenic flexure. A laceration, 2 cm. long was present on the concave surface of the spleen and blood was slowly oozing from it. There was less than 50 cc. of free intraperitoneal blood present. Ecchymosis in the left retroperitoneal tissues gave one the impression of slight bleeding in the left perirenal area. No other evidence of injury

was found. Splenectomy was performed, and the patient made an uneventful recovery. The hematuria ceased after the first day.

Postoperative roentgenologic studies showed gas present in the stomach, with a smooth greater curvature (Fig. 4). Excretory urograms showed a normal urinary tract.

Case 3.—N.C.B. No. 28421 (From the Service of Dr. Fred K. Garvey): E. M. C., white, female, age 11, was admitted at 4:15 P.M., May 22, 1944, with a history that

FIG. 3.—Preoperative film of abdomen of Case 2, showing the gas in stomach, serrated greater curvature and enlarged splenic shadow.

she had been kicked in the left flank by a mule four hours earlier. She had fainted several times before being brought to the hospital. When examined in the Emergency Room her temperature was 97.8° F. per rectum, pulse 160; blood pressure 50/0. There was splinting of the left diaphragm, with definite respiratory lag on the left. Examination of the thorax was negative. Her abdomen was moderately distended, and acutely tender, but not rigid over the left side. There was a large elevated and contused area in the left costovertebral angle, and this area was exquisitely tender. The urinary bladder could be percussed three fingers breadth above the symphysis pubis. The patient voided 400 cc. of grossly bloody urine, which clotted in four minutes.

Accessory clinical findings showed a hemoglobin of 9.5 Gm.; red cells 4,200,000; white cells 16,800.

A plain film of the abdomen showed marked gaseous distention of the stomach, with very little gas in the small or large bowel. The right kidney and psoas shadows were normal. The left kidney shadow was obliterated, and the left psoas shadow obscured by an increased soft-tissue density in this region (Fig. 5). An intravenous urogram showed normal excretory function on the right, with complete absence of function of the left kidney (Fig. 6).

FIG. 4.—Postoperative film of abdomen of Case 2, showing stomach normal in position, with much gas in it, but a smooth greater curvature.

The patient received blood and plasma and an exploratory celiotomy was performed through a left flank incision. The left kidney was found to be shattered into four pieces, with much clot under tension within Gerota's fascia, and a partial tear of the renal artery and vein. Nephrectomy was performed. The diaphragm was normal, and the tissues adjacent to the posterior surface of the left colon were edematous. The peritoneal cavity was opened and found free of blood, with a normal spleen and normal bowel. The patient was in moderately severe circulatory failure on the table and at the conclusion of the procedure her blood pressure was 90/60. Her postoperative course was uneventful; and she was discharged on her twelfth postoperative day. Plain films of the abdomen, made postoperatively, revealed her stomach normal in position and containing a small amount of gas. The small part of the greater curvature that could be visualized was smooth.

In these three patients, one had a lacerated spleen and two fractured ribs, with no evidence of any other lesion; and her plain film demonstrated very clearly the signs described by Solis-Cohen and Levine. The second patient with laceration of the spleen as well as damage to the left kidney also had the characteristic roentgenographic findings. The third patient with a shattered kidney and a normal spleen, had much gas in the stomach

FIG. 5.—Preoperative film of abdomen of Case 3, showing marked gaseous distention of the stomach with smooth greater curvature. Right psoas shadow is normal; left psoas shadow is obliterated.

but a smooth greater curvature, along with obliteration of the left kidney shadow, and an obscure left psoas shadow.

These facts stand as evidence that the gas-containing stomach, with the serrated greater curvature, will show on a plain film of the abdomen when the splenic laceration is small or moderately large; that these findings still occur when some other viscus in addition to the spleen is injured; that these signs are absent when the kidney is ruptured in the presence of a normal spleen, and that they are not present following splenectomy.

The cause of these roentgenographic findings is not clear. A notched, indented or slightly serrated greater curvature may appear occasionally in a plain abdominal film of a patient who has not been subjected to any trauma. Some of these shadows are due to extrinsic masses pressing on the stomach, and some of them are of unknown etiology. Obviously, in such instances the differential diagnosis will rest on the absence of any history of injury or the finding of some extragastric mass. Solis-Cohen and Levine feel that,

FIG. 6.—Preoperative excretory urogram of Case 3. Stomach appears the same as in Figure 5. Note absence of excretion of dye by the left kidney.

in a patient who has a lacerated spleen, the gravitation of blood along the gastrosplenic ligament adjacent to the greater curvature is the cause of the serrations seen in the stomach shadow. This could explain the findings in Case 1, but it does not explain them in Case 2, where there was not enough hemorrhage to infiltrate the gastrosplenic ligament.

In Cases 1 and 2 with minimal to moderately severe splenic injury and equivocal clinical findings, the plain films raised strong suspicions that the spleen was lacerated. Once such a suspicion exists, celiotomy is indicated, unless both surgeon and patient are willing to tolerate the anxiety, as well as the danger, that a delayed rupture may occur.

Further experience with these roentgenographic findings in the presence

of damaged spleens is necessary. These patients are offered as evidence to corroborate the findings of Solis-Cohen and Levine, and to stress the importance of plain films of the abdomen and chest when splenic damage is suspected, not alone to help evaluate the injury to the spleen, but to help rule in or out associated thoracic injuries.

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SULFONAMIDE THERAPY IN CLEAN THORACOPLASTY CASES

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The employment of the sulfonamides in clean operative cases to prevent wound infections has not been completely successful. Most of the publications regarding the procedure state that some infections have occurred despite the prophylactic use of the drugs. If the sulfonamides have not prevented infections in clean wounds, then of what value is their routine prophylactic employment?

The experience of the Tuberculosis Service at Bellevue Hospital, with the use of the sulfonamides in clean thoracoplasty operations, merits publication. Our report concerns 83 patients who had 203 clean thoracoplasty operations, of which 167 were for parenchymal disease and 36 were for mixed empyemas with bronchopleural fistulae. All of the thoracoplasty operations in the series were clean even though some of the operative procedures in the empyema group approached an infected area. The modern thoracoplasty operation, averaging three ribs a stage, was performed in almost every case, and, generally, silk ligature and suture materials were used throughout. The authors assisted, or performed, most of the operations and observed the patients' convalescence; while the selection of cases for local, oral and nonsulfonamide therapy was determined by the surgical attending staff.

The thoracoplasty cases were grouped into three series: those which had the sulfonamides applied locally, those which received the sulfonamides orally, and the controls in which no sulfonamides were used. In this manner the groups may be compared and contrasted from the data presented. The scope of our investigation includes the patients' local and systemic reactions to the sulfonamides, the blood and wound fluid sulfonamide concentrations when the drugs were employed locally and perorally, and the incidence of contaminations and infections in the clean operative wounds of the different groups.

The first series consisted of 97 cases in which the sulfonamides were applied locally to the thoracoplasty wounds. The sulfonamides were prepared and sterilized in two-, four- and six-gram amounts, with an average of 4.7 Gm. being used per operation. In each, the drug was dusted evenly, without lumping, over the wound surface including the subcutaneous tissues.

No known toxic reactions occurred in any of the cases and there was no evidence of poor or delayed wound healing. Twenty cases of the series of 97 were reviewed to determine the volume of excess wound fluid which was

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aspirated. All 20 cases formed excess wound serum, and the average amount aspirated per case was 328 cc.

The second series of thoracoplasty cases numbered 39, and they received the sulfonamides orally in divided doses for three or four days after the operation. One patient developed jaundice and anemia, which disappeared after the drug was withdrawn and three other patients had hematuria and urinary sulfonamide concretions, but no appreciable oliguria. All wounds appeared healed at the tenth postoperative day. Six of the ten cases analyzed for excess wound fluid had excess fluid and about 135 cc. were aspirated in each of the six cases.

The third series was composed of 67 thoracoplasty cases in which no sulfonamides were used, and they acted as the control group. There were no reactions resembling sulfonamide toxicity and all wounds healed promptly. Fifteen cases of the group were examined for excess wound serum and the eight cases which developed excess serum averaged 110 cc.

The three series revealed that the systemic reactions to the sulfonamides occurred only in the group which received the drug perorally, especially in large amounts. No evidence of nonhealing, or even any delay of wound healing, was observed in any case. Excess wound serum exudation occurred in each series, but it was seen more often and of greater volumes in the series of cases which had a sulfonamide applied locally in the thoracoplasty wound.

The wound fluid was aspirated, usually between the second and the fifth postoperative days, from the subscapular space, which was enlarged as a result of the operative procedure. Wound serum sulfonamide concentrations were determined in many of the thoracoplasty cases in which the drugs were applied locally, and the concentrations were so surprisingly low that an investigation of the comparative concentrations in blood and wound fluid was undertaken. Thereafter, sulfonamide levels were determined on each specimen of aspirated wound fluid, while blood samples were drawn at eight, 24 and 48 hours postoperatively. The completed data on 25 thoracoplasty cases in which the sulfonamides were implanted locally were reviewed and the average of the blood and wound serum concentrations are shown in Chart I.

It was assumed from the trend of averages that the peak of the blood sulfanilamide levels occurred before the eight hour specimens were drawn, while the blood sulfadiazine concentrations peaked between the eight- and 24-hour specimens. Likewise, it was assumed that the wound serum sulfonamide concentrations were undoubtedly high immediately after the operation, but they rapidly declined approximating one milligram for each gram of drug applied locally at 24 hours and being insignificant after the fourth day.

We felt that six to eight milligrams of sulfonamide in each 100 cc. of fluid was necessary for the optimal therapeutic effect, if wound infections were to be prevented. We sought to secure these higher concentrations of the sulfonamides by returning to the systemic administration, as that method

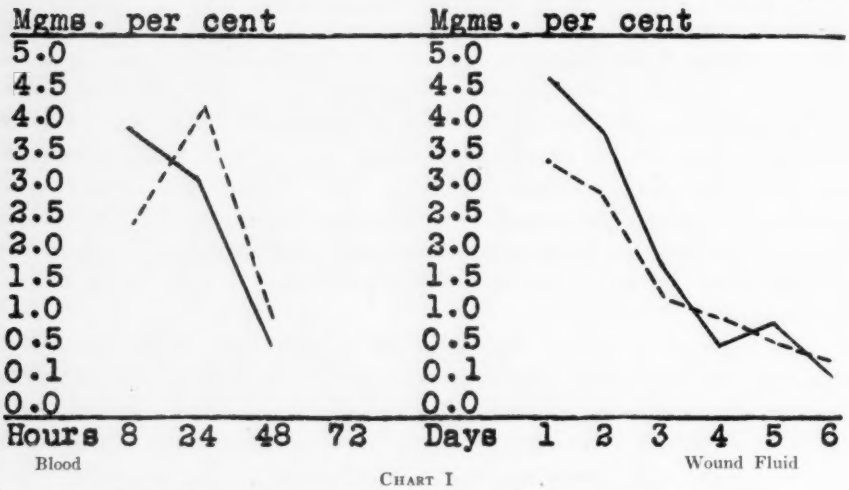

CHART I

Average of Blood and Wound Fluid Sulfonamide Concentrations in the Local Application of Sulfonamides in 25 Thoracoplasty Cases

Sulfanilamide averaged 4.6 grams in wound per 16 cases. Sulfadiazine averaged 3.7 grams in wound per nine cases. Sulfanilamide indicated by solid line. Sulfadiazine indicated by broken line.

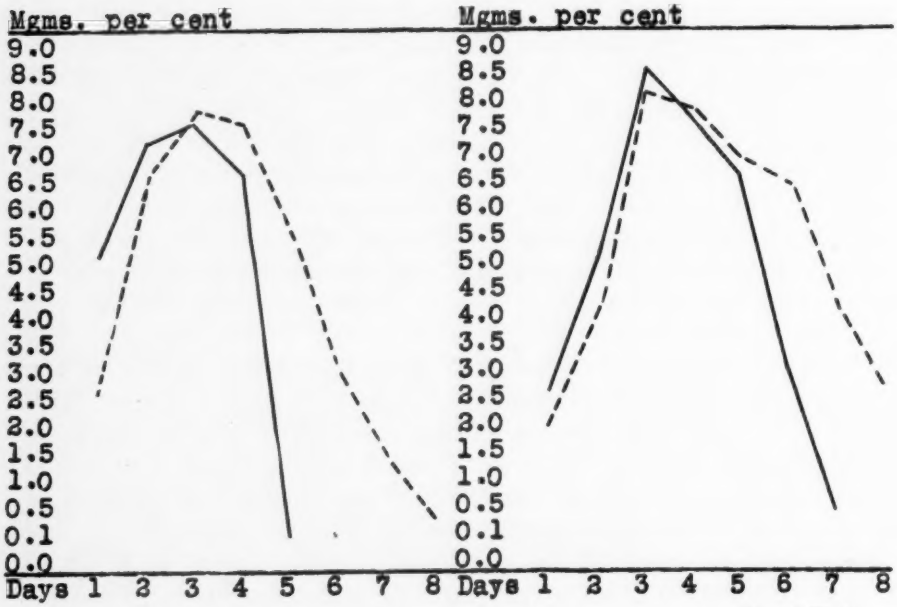

CHART II

Average of Blood and Wound Fluid Sulfonamide Concentrations in the Peroral Administration of Sulfonamides in 21 Thoracoplasty Cases

Sulfanilamide averaged 20 grams perorally in six cases. Sulfadiazine averaged 26 grams perorally in 15 cases. Sulfanilamide indicated by solid line. Sulfadiazine indicated by broken line.

had given satisfactory results in other cases. With this in mind, some of the thoracoplasty cases were given two grams of a sulfonamide by mouth shortly after their operation and then one gram every four hours for three or four days. No case was included if a sulfonamide had been applied locally to the wound. Blood for a sulfonamide level was drawn at the same time that wound fluid was aspirated so that a comparison of the concentrations of the drugs could be made. The data on 21 thoracoplasty cases which received a sulfonamide orally were reviewed and the average blood and wound serum concentrations are shown in Chart II.

The peroral administration of sulfanilamide and sulfadiazine produced good concentrations in the blood stream. The sulfanilamide levels rose and fell rapidly, while the peak sulfadiazine levels occurred later and fell less rapidly. Similar concentrations of sulfanilamide and sulfadiazine were found in the wound fluids, but, again, the fall of the sulfadiazine concentrations were slower. The difference in the concentration trends can be explained by the more rapid absorption and the greater diffusibility of sulfanilamide over sulfadiazine. It was worthy of note that the peak wound fluid sulfonamide concentrations, as a rule, exceeded the peak blood sulfonamide values. In one unusual case the blood sulfonamide levels reached 8.1 mg. per cent on the fourth postoperative day, while at the same time the wound fluid sulfonamide concentration was 105 mg. per cent.

Comparison and contrast of the two series revealed that the local implantation of the sulfonamides yielded immediate high wound serum levels, which rapidly decreased to subtherapeutic values and moderately high blood concentrations that fell even more rapidly; whereas, the peroral administration of the sulfonamides produced, after a short lag interval, high wound fluid and blood concentrations which could be sustained by the oral administration of the drugs. From this it would appear that the immediate, high concentrations of the sulfonamides would be more efficacious than the delayed high concentrations as seen in the oral administration method, but, clinically, less infections occurred when the sulfonamide levels exceeded five milligrams per cent for several days.

The infections in our series of thoracoplasty cases were separated into superficial and deep. The superficial infections occurred above the muscle layers of the shoulder and in the subcutaneous tissues. The superficial infections were mild and never invaded the deeper structures; while the deep infections, which were more severe, occurred beneath the muscle layers of the shoulder and always involved the enlarged, deep subscapular space. Not included in the series were four tuberculous chest wall infections which were believed to have started from a needle tract abscess and one subscapular space infection which followed the rupture of a tuberculous cavity during a revision thoracoplasty operation. These infections delayed or prohibited further surgical collapse measures.

The incidence of pyogenic infections in 203 clean thoracoplasty cases was 5.4 per cent. They range from minor stitch abscesses to severe subscapular

TABLE I

THE SULFONAMIDES USED; THEIR MANNER OF EMPLOYMENT AND THE AREAS INFECTED IN 203 CLEAN THORACOPLASTY CASES

Group	Sulfonamide	Cases	Infections		
			Superficial	Deep	Per Cent
Local	Sulfanilamide	79	3	2	6.3
	Sulfadiazine	13	1	1	15.3
	Sulfathiazole	5	0	0	0.0
Oral	Sulfanilamide	27	1	0	3.7
	Sulfadiazine	12	0	0	0.0
Control	None	67	3	0	4.5
Total		203	8	3	5.4

space infections. The sulfonamides used, their manner of employment and the areas infected are shown in Table I.

The variations in the incidence of infections in the different groups of thoracoplasty cases required further investigation to determine if a greater percentage of wounds in any one group became contaminated. Cultures of the operative wound and the aspirated wound fluid were relied upon as evidence of contamination in lieu of the actual infection and, even then, some were probably missed. The identification of the bacterial contaminants was also desired as a guide to the possible sources of contamination and to the ability of the sulfonamides to prevent specific bacterial infections. We felt that a better evaluation of sulfonamide therapy in clean wounds could be made if the protective ability of the drugs were known.

We reviewed the operative wound, the wound fluid and the infected wound culture reports on the 203 clean thoracoplasty cases and found that 191 were satisfactory for analysis. In the series of 191 analyzed

TABLE II

NUMBER OF CONTAMINATED WOUNDS; NUMBER OF INFECTED WOUNDS AND THE BACTERIA IDENTIFIED IN 191 THORACOPLASTY CASES

Topics Analyzed in Each Series	Local		Oral	Control	Total
	Sa*	Sd†	Sa	None	
Cases reviewed	73	12	25	64	191
Cases contaminated‡	11	3	4	7	25
Cases infected	5	2	1	3	11
Bacterial contaminants					
Staph. albus	4(0)			2(0)	6(0)
Staph. albus hemolyticus	1(1)	1(1)	1(0)	2(1)	5(3)
Staph. aureus	1(1)		2(1)	2(1)	5(3)
Staph. aureus hemolyticus	3(3)	1(1)	1(0)	1(1)	6(5)
Strept. gamma	1(0)	1(0)			2(0)
Strept. beta hemolyticus	1(0)				1(0)

*Sa = sulfanilamide. †Sd = sulfadiazine.

‡ Contamination determined by cultures or the occurrence of an infection. ( ) Signifies number of infections.

cases, 20 operative wound cultures were reported positive for pyogenic bacteria and four of them had, in addition, a positive culture of the wound serum. One of the four cases developed a deep wound infection, and five of the remaining 16 cases had superficial infections. Two other cases had sterile operative wound cultures, but later had positive wound fluid cultures, and both developed deep wound infections. Three additional

cases had sterile operative wound and wound fluid cultures, but superficial infections occurred in each.

The number of contaminated wounds, the number of infected wounds, and the bacteria identified are shown in Table II.

The percentage of thoracoplasty wounds which showed contamination were similar except for the groups, local sulfathiazole and oral sulfadiazine. They had no positive operative wound or wound fluid cultures and no infections occurred. Eleven of the 25 contaminated wounds developed infections, an incidence of 44 per cent; while a comparison of the sulfonamide treated and the control groups showed they had a similar incidence. A further breakdown of the groups revealed that only one infection occurred in the four contaminated wounds treated with sulfanilamide orally; while two of the three contaminated wounds having a local application of sulfadiazine became infected.

All of the bacterial contaminants were cocci. The staphylococci made up the majority of the bacteria, with the *Staphylococci albus* and *aureus hemolyticus* being the most common. Only three streptococcal contaminations were observed and one of these was the hemolytic streptococcus. The identified bacteria suggested that the greatest sources of contamination were the skin, neighboring infected wounds and the nose and throat of the operating personnel. The protective ability of the sulfonamides was the greatest in the streptococcal group and the least in the staphylococcal bacteria, especially *Staphylococcus aureus hemolyticus*. A further estimation of the drug's protective ability was impossible in the small number of cases.

Comment.—The popularity and the widespread use of the sulfonamides in surgical cases is reflected in the literature. Some publications reported excellent results with the sulfonamides locally, while others stated that the systemic administration was the most beneficial. Many articles advocated the employment of the sulfonamide compounds in contaminated and infected cases, especially the local application in abdominal surgery; while a few recommended it routinely as a prophylaxis in clean surgical cases. Along with the publications of the good results of sulfonamide therapy have appeared articles reporting the unfavorable aspects as drug toxicity, the development of sensitivity reactions and the occurrence of fatalities from the use of the sulfonamides. The evaluation of sulfonamide therapy in clean surgical wounds must cover both sides.

Meleney,[3] in 1944, discussed the problems of evaluating drug therapy in surgical infections. He outlined plans for comparing treated cases in which the numerous factors that influence infections in wounds could be grouped so as to satisfy the most exacting biostatistician. For a drug to be remarkable, its action would have to be clear-cut or the results brilliant. The difficulties in executing the plans are appreciated, but until it is done we must rely on clinical experience.

Harrison and Berry,[1] in 1943, analyzed the results of approximately 430 thoracoplasty cases of tuberculosis at Bellevue Hospital which were per-

formed prior to our series. They stated that the local application of sulfanilamide and sulfadiazine was advantageous in preventing wound infections, and they found no ill effects except excess wound serum exudation. We feel that excess wound serum in the thoracoplasty wound is harmful for it discomforts the patient; often produces necrosis of wound edges unless removed; and the removal by aspiration offers another potential source of bacterial contamination.

The data presented by Harrison and Berry was insufficient for comparing the treated and untreated cases, but they did mention that six minor and four deep wound infections occurred in the clean parenchymal group. Two of the six minor and two of the four deep wound infections developed despite local sulfonamide therapy. Two of the four deep wound infections, however, followed the rupture of a tuberculous cavity and perhaps should not be considered in this respect. The combined incidence of infections in the clean parenchymal group of thoracoplasty cases was 3.4 per cent; while in the empyema group, which has a higher risk of contaminations, it was seven per cent.

About the same time, Long[2] reviewed and summarized the use of the sulfonamide compounds in the prevention and treatment of wound infections. He warned that the sulfonamides, which are an adjunct to surgical therapy, should not be relied upon to cover negligent surgical judgment and technic. He stated that important toxic reactions as fever, acute hemolytic anemia, renal complications, and others occurred in the course of systemic sulfonamide therapy about as follows: sulfanilamide 11.9 per cent, sulfapyridine 15.9 per cent, sulfathiazole 18.6 per cent and sulfadiazine 6.5 per cent. He added that sulfadiazine, which produces the fewest toxic reactions, was responsible for hematuria in 1.7 per cent of treated patients; while the next best drug, sulfanilamide, produced an acute hemolytic anemia in about two per cent of treated patients.

Long analyzed the evidence regarding the local effects of applying the sulfonamides in the wound. He found that wound fluid exudation often formed and if the wound was tightly sutured some necrosis may result. He added that some investigators reported an inflammatory response to the drugs which increased with the less soluble sulfonamides. Often, the inflammatory picture simulated foreign body reactions; especially when large coarse crystals or finely powdered drugs that caked were used. In some articles the wound reactions were interpreted as delayed or poor wound healing.

Long believed that the peroral administration of sulfadiazine, with blood concentrations of four to seven milligrams per cent, coupled with the local application of sulfanilamide offered the best chance for the prevention of wound infections. He felt that sulfanilamide's high solubility, its wide range of bacterial effectiveness and the moderately low degree of associated toxicity made it suitable for local use. Similarly, he selected sulfadiazine for its properties of slow diffusion, wide bacterial range and minimal toxicity for

the oral employment. He added that the peroral administration of the drugs could be stopped after five to seven days in the absence of an infection and the topical application need be continued only in open wounds to prevent secondary invaders.

It does not appear logical to subject clean thoracoplasty wounds to routine prophylactic sulfonamide therapy, as only a small portion become contaminated and even a smaller number develop infections. The occurrence of excessive wound fluid with the local application and the occasional toxic reactions with the oral administration of sulfonamide therapy seems more hazardous than the infrequent, severe infections. If contamination of the thoracoplasty wound could be predicted then either the local or the systemic, or a combination of both methods of administering the drugs, might be employed advantageously; but as most contaminations are slight only bacteriologic studies are reliable indicators. Thus, the rationale of employing the sulfonamides in clean thoracoplasty cases revolves around the potential or actual contamination of the wound.

The antibacterial action of the sulfonamides is the most active against the streptococci. All of the sulfonamide compounds are thought to be about equally effective and their selection is determined largely by the properties of the drugs. The bacteriostatic action of the sulfonamides against the staphylococci is less active and some believe that sulfathiazole is the best while others prefer sulfadiazine. In the latter, it is well-recognized that the systemic use of the drug has proved to be effective against the common contaminating bacteria of wounds.

We suggest, that instead of the routine prophylactic employment of the sulfonamides in clean thoracoplasty cases, the drugs be used only in potentially contaminated cases. We believe that local plus systemic therapy is warranted when gross soiling or some other accident happens to contaminate the wound. Wounds that may become contaminated, as those near an infected area, or when an unusual high incidence of contaminations are occurring, should have the drug applied locally and if the cultures are positive, then the systemic administration of the drug can be started. Again, the sulfonamides should be administered systemically if the bacteriologic studies of the wound or wound fluid reveal contamination, or the patient shows evidence of infection as by unusual temperature elevation or localized wound cellulitis. We feel these indications for sulfonamide therapy in clean thoracoplasty wounds are more efficacious and less dangerous than the routine prophylactic employment of the drugs. Certainly, the lessening of contamination, the application of approved surgical technic and the active maintenance of the patient's defense mechanism is of greater importance in the prevention of clean wound infections than is the present use of the sulfonamide compounds.

SUMMARY

The comparison of local and oral sulfonamide therapy in clean thoracoplasty cases revealed some undesirable features not seen in the untreated cases. The excessive wound fluid formation in local and the toxic reactions

in oral therapy were the chief disadvantages. The local and the peroral employment of the sulfonamides produced predictable drug concentration trends in the blood and the wound serum. The first was immediate and short, while the second was delayed and sustained. Infections followed contaminations in each series, the lowest being in oral sulfonamides, then the controls and the highest was local sulfonamides. The logic of employing the sulfonamides in clean thoracoplasty cases was discussed and our suggestions for the use of the drugs were outlined.

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UROLOGY AWARD.—The American Urological Association offers an annual award "not to exceed $500" for an essay (or essays) on the result of some specific clinical or laboratory research in Urology. The amount of the prize is based on the merits of the work presented, and if the Committee on Scientific Research deem none of the offerings worthy, no award will be made. Competitors shall be limited to residents in urology in recognized hospitals and to urologists who have been in such specific practice for not more than five years. All interested should write the Secretary, for full particulars.

The selected essay (or essays) will appear on the program of the forthcoming June meeting of the American Urological Association.

Essays must be in the hands of the Secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis, Tennessee, on or before March 15, 1945.

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